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MODEL STUDIES RELATED TO FREDERICAMYCIN A
AND
USE OF INTRAMOLECULAR HYDROGEN ABSTRACTION IN ORGANIC SYNTHESIS

BY
MICHEL CANTIN ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta
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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled MODEL STUDIES RELATED TO FREDERICAMYCIN A AND USE OF INTRAMOLECULAR HYDROGEN ABSTRACTION IN ORGANIC SYNTHESIS submitted by MICHEL CANTIN in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

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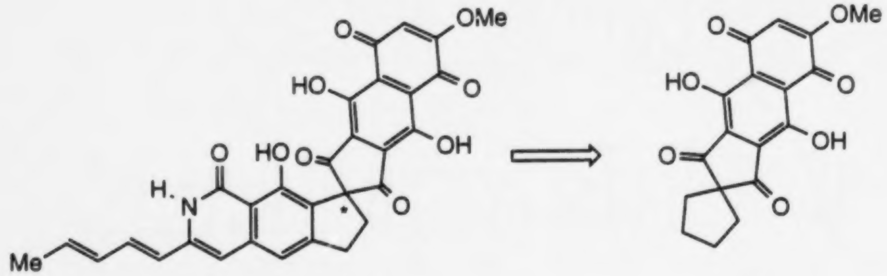
Date: 16 November 1994

Cette thèse est dédiée à la mémoire de mon grand-père, Fernando Lavigne (1917-1994), décédé mardi le 2 août 1994 à l'Hôtel Dieu d'Arthabaska, à la suite d'une longue maladie.

ABSTRACT

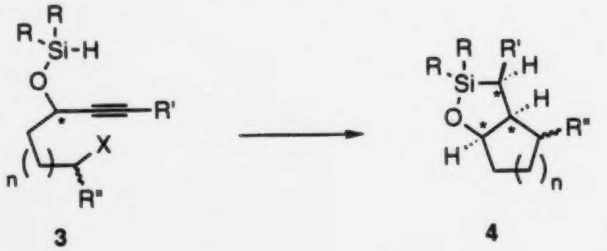
The first part of this thesis describes the synthesis of compound **2**, representing four of the six rings of the antitumor agent Fredericamycin A **1** (Scheme A). The spiro center (*) of this molecule was built by radical cyclization methodology. The route followed was developed previously in this group, but introduced the use of isotope to suppress a side reaction.



1 **2**

Scheme A

In the second chapter, the possibility of the use of intramolecular radical transfer (hydrogen abstraction) in organic synthesis was explored. This study led to the discovery of a new radical reaction (**3**→**4**, Scheme B), which involves an initial *exo-dig*-radical cyclization, followed by intramolecular hydrogen abstraction and terminated by a 5-*endo-trig*-radical cyclization of the silicon radical. In this tandem process, a bicyclic product is generally isolated, in which its three centers of asymmetry (*) were fully controlled by only one center in the radical cyclization precursor **3**.



3 **4**

Scheme B

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LIST OF ABBREVIATIONS

AIBN	2,2'-azobisisobutyronitrile
9-BBN-H	9-borabicyclo[3.3.1]nonane
BnBr	benzyl bromide
CAN	ceric ammonium nitrate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
MOMCl (CH_3OCH_2Cl)	methoxymethyl choride
$Py\cdot HBr\cdot Br_2$	pyridinium bromide perbromide
PCC	pyridinium chlorochromate
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TMSOTf	trimethylsilyl trifluromethanesulfonate
p-$TsOCD_3$	methyl- d_3 *p*-toluenesulfonate
p-$TsOH\cdot H_2O$	*p*-toluenesulfonic acid monohydrate

Part 1

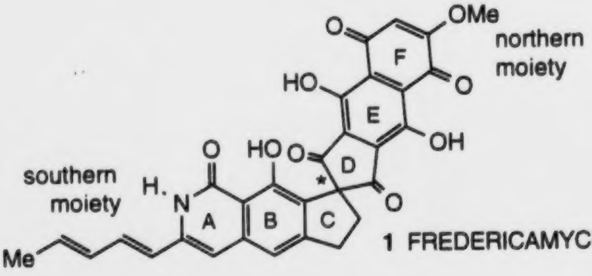
MODEL STUDIES TOWARDS FREDERICAMYCIN A

I INTRODUCTION

General Aspects

Fredericamycin A was isolated from a strain of *Streptomyces griseus* from a soil sample in Frederick, Maryland.[1] The interest of the scientific and medical community in this new natural compound originated with biological tests showing its potential as a chemotherapeutic agent against cancer.[2] *In vitro*, fredericamycin A is very cytotoxic against P388 and L1210 mouse leukemia cells and human glioblestoma cells. *In vivo*, this new antitumor agent was shown to be active against the P388 ascites tumor, the mammary CD8F tumor, and to have marginal activity against the B16 melanoma tumor.[3]

The structure of fredericamycin A **1**[4] was assigned unequivocally by X-ray crystallographic determination,[5] and was confirmed later, not without difficulty,[6] by spectroscopic and mass spectral characterization. These measurements, however, did not permit the determination of the absolute configuration for the single center of asymmetry (*) of fredericamycin A.



1 FREDERICAMYCIN A

The unique architecture of this antibiotic consists of two subunits; the southern part (rings A, B, and C) is composed of an isoquinoline unit, and the quinone of the northern moiety (rings D, E, F) which one might suspect as being crucially involved in the biological activity.[7] A spiro[4.4]nonane ring system (rings C and D) gives the molecule its characteristic L-shape, and also holds the two arms in a quasi perpendicular relationship to one another.

The biosynthesis of fredericamycin A adopts the polyketide pathway,[8] although whether one or two chains are involved in assembly of the molecule has not yet been established.

Fredericamycin A, whose planar subunits resemble DNA-intercalating of drugs, inhibits both DNA topoisomerases I and II and DNA polymerase α.[9] However, knowledge of diverse modes of action of fredericamycin A does not allow clarification of its mechanism of antitumor effects. In fact, some controversy[10] exists concerning the proposal of spontaneous generation of some reactive free radical forms of the drug.

The low water-solubility of fredericamycin A was considered to be a serious deterrent for the preparation of pharmaceutical compositions. Fortunately, water soluble salts of fredericamycin A retain the original biological activity.[11]

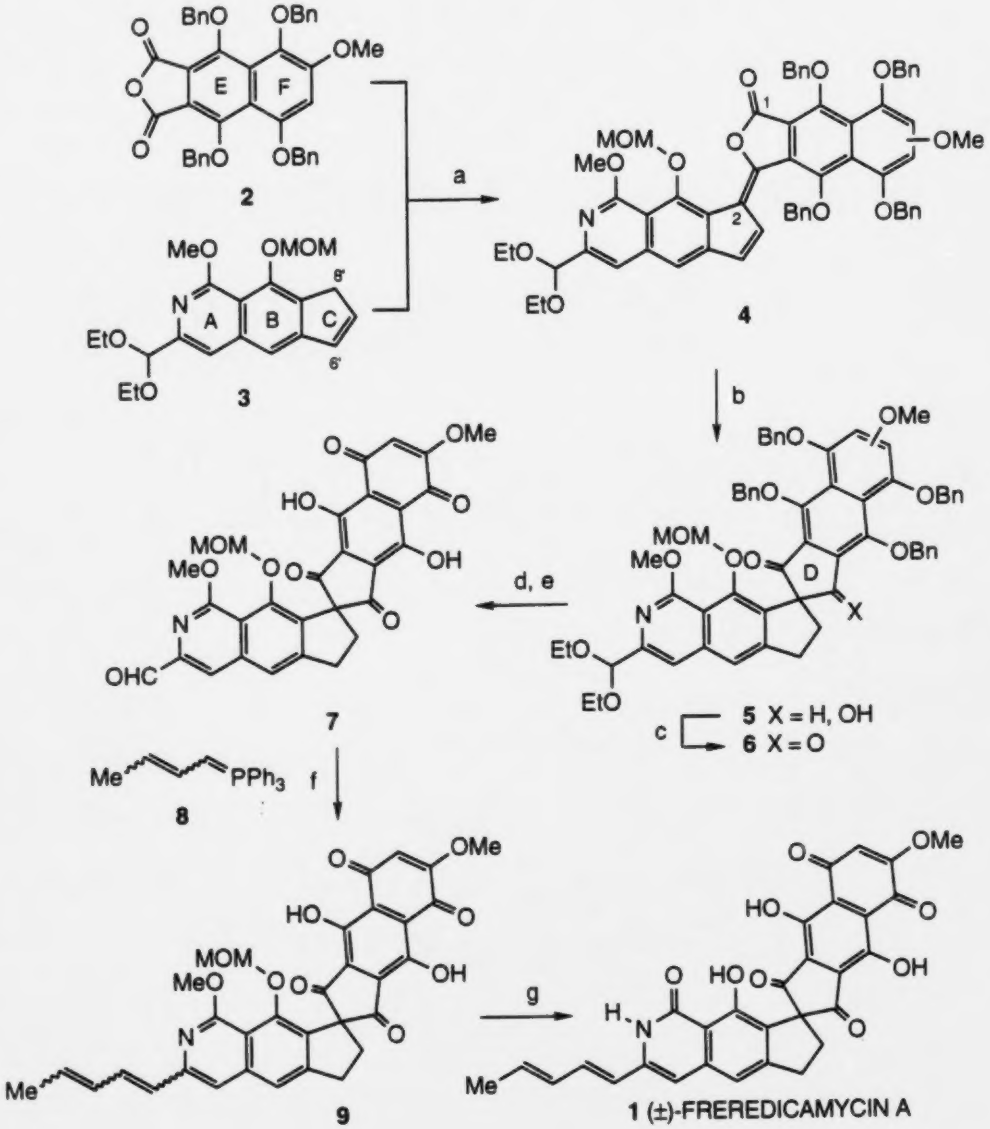
Synthetic Approaches to Fredericamycin A

Since the publication of the unique structure and biological properties of the new antitumor agent, several reports describe a wide range of approaches to the partial or total synthesis of fredericamycin A. The construction of its spiro center was readily recognized by organic chemists as one of the synthetic challenges of this molecule. At the time of the discovery of fredericamycin A, no existing method for the construction of quaternary centers provided directly the spiro[4.4]nonane portion of fredericamycin A.[12]

Although many publications[13,14] describe the preparation of portions of fredericamycin A which exclude the formation of the quaternary carbon, the emphasis of this Introduction will be on new methodologies that emerged from tackling the formation of the spiro center.

Construction of Ring D of the Fredericamycin A Spiro Center

Intramolecular Aldol Condensation



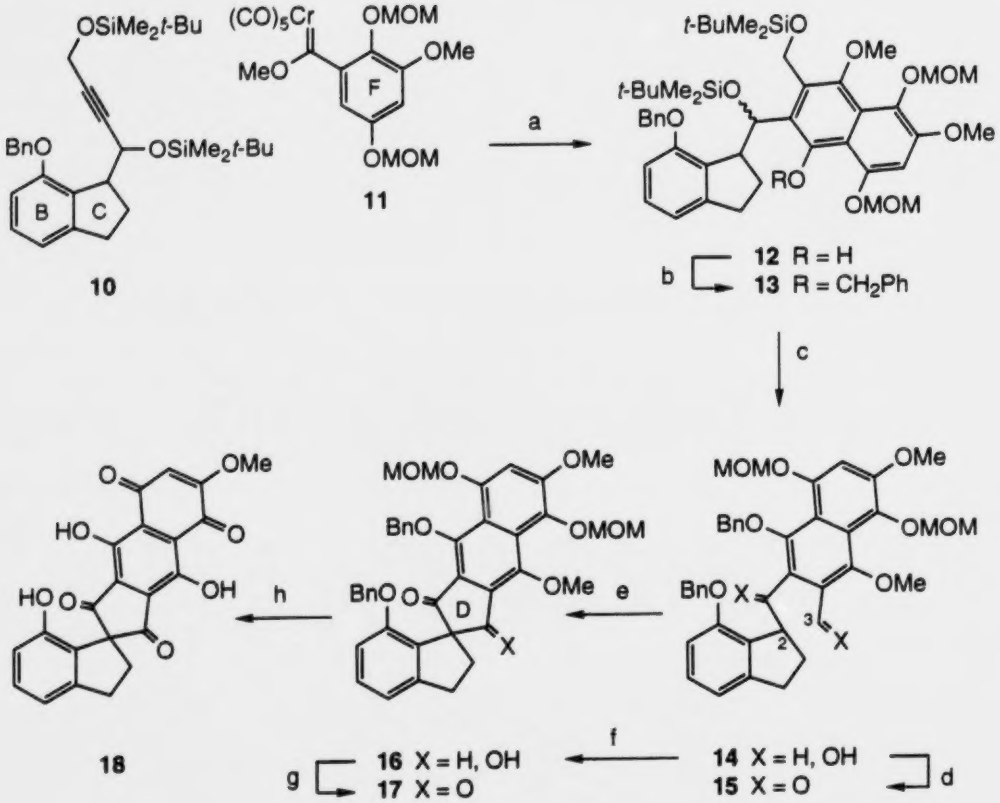
Scheme 1 *Reagents and conditions:* (a) 2.1 equiv of *t*-BuLi, THF, -78 °C, 5 min; then 1.02 equiv of Me_3SiCl, -78 °C, 15 min; then **2**, THF, -78 °C, slow addition 10 min; -78 °C, 45 min, 81% (b) DIBAL-H, CH_2Cl_2, -78 °C, 20 min; (c) $(COCl)_2$, DMSO, Et_3N, -78 °C, 50% (two steps); (d) 1 atm H_2, 10% Pd/C, EtOH/AcOH (10:1), 4 h; air, 1 h; (e) 0.015 M HCl, acetone/THF (1:1), rt, 2 h, 71% (2 steps); (f) 3.45 equiv of **8**, THF, -78 °C, 10 min, 21%; (g) NaBr, *p*-TsOH, I_2, MeOH, reflux, 20 min, 53% (reference 15b)

Kelly[15] reported the first total synthesis of racemic fredericamycin A (Scheme 1). In his convergent synthetic approach, the spiro center was constructed by an intramolecular aldol reaction. During the coupling of the ambident anion of isoquinoline **3** and anhydride **2**, a silicon group (Me_3Si-) was momentarily introduced at the more reactive 6' position[16] in order to direct the coupling to the desired 8' position. Reduction of lactone **4** induced formation of ring D via intramolecular aldol condensation by making the bond between carbons 1 and 2, and the epimeric mixture of alcohols **5** was oxidized to diketone **6**. After some partial deprotection and oxidation of the northern moiety (**6**→**7**), the pentadienyl tail was introduced (**7**→**9**) in rather poor yield. The first total synthesis of fredericamycin A was completed by removal of the remaining protective groups in the southern moiety (**9**→**1**) and by chromatographic isolation of the natural isomer (from a mixture of isomeric dienes).

Boger[17] similarly utilized an intramolecular aldol condensation for the construction of the spiro center (Scheme 2). An alkyne-chromium carbene complex was used for the annulation that connected regiospecifically alkyne **10** with the carbenoid **11**. The phenolic hydroxyl of the resulting mixture of isomers **12** was protected as a benzyl ether prior to conversion into diols **14** by treatment with fluoride ion. In order to build ring D, two routes using the aldol condensation were developed, either directly (**14**→**16**) or with isolation of the intermediate ketoaldehyde (**14**→**15**→**16**). Further oxidation and deprotection (**16**→**17**→**18**) gave a substantial model of fredericamycin A, with the desired level of oxidation. A recent publication by Boger described the synthesis of the southern part[13e] of the antitumor agent.

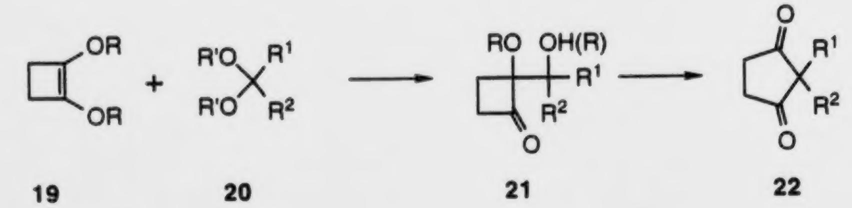
Kuwajima Reaction

A general method for construction of 1,3-cyclopentanediones was introduced in 1984.[18] The Lewis acid catalyzed aldol-type reaction of 1,2-bis(trimethylsiloxy)-cyclobutene **19** and acetal **20** produced succinoin derivative **21** which underwent an



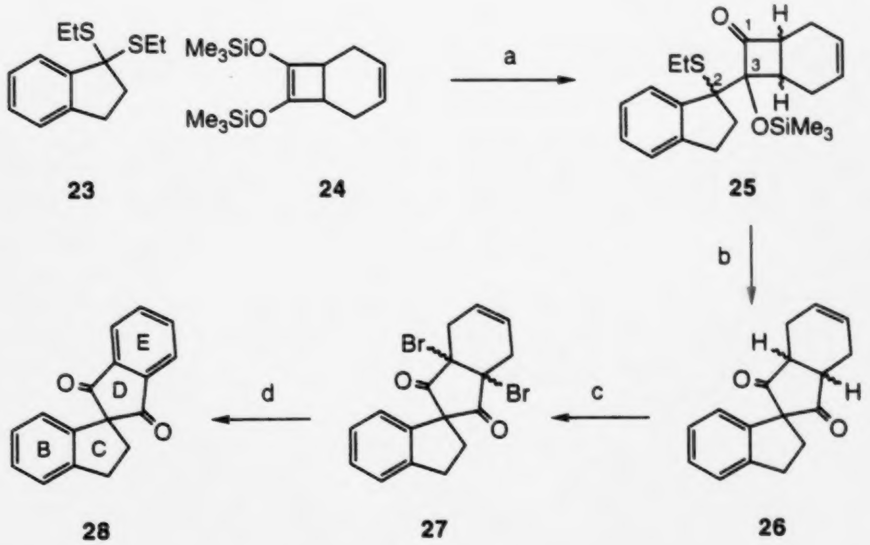
Scheme 2 *Reagents and conditions:* (a) Ac_2O, heptene, 80 °C, 48 h, 48%; (b) 3 equiv of $PhCH_2Br$, 10 equiv of K_2CO_3, acetone, 55 °C, 64 h, 78%; (c) *n*-Bu_4NF, THF, 55 °C, 14 h, 89%; (d) DMSO, $(COCl)_2$, CH_2Cl_2, -64°C, 5 min, **14**, -64 °C, 15 min, Et_3N, -64 °C, 5 min, rt, 20 min, 43%; (e) MeONa, MeOH, 65 °C, 5.5 h, 82%; (f) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 15 min, **14**, -78 °C, 2 h, DBU, then rt, 5.5 h, 58%; (g) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 15 min, **16**, -78 °C, 1 h, Et_3N, then rt, 40 min, 75%; (h) BBr_3, CH_2Cl_2, -78 °C, 40 min, 74% (reference 17c)

acid-catalyzed rearrangement to give 1,3-cyclopentanediones **22** via the ring expansion of the cyclobutane ring (Scheme 3).



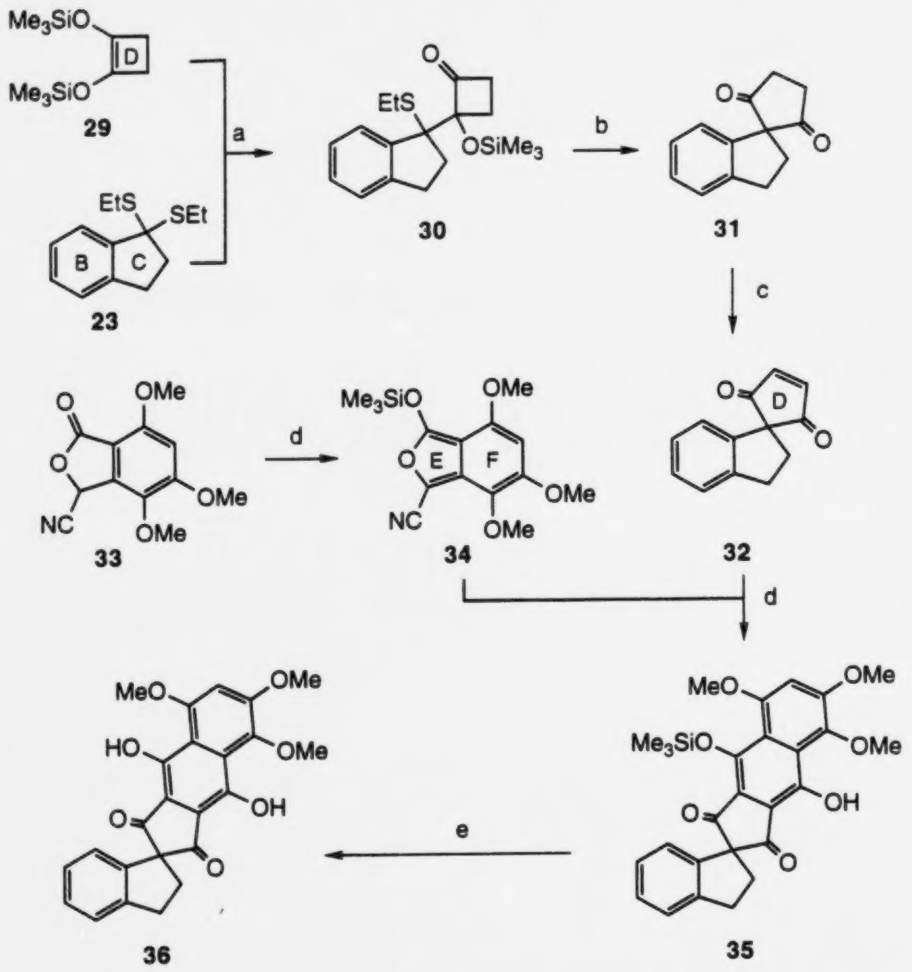
Scheme 3

The usefulness of the Kuwajima reaction for the construction of the spiro center of fredericamycin A was demonstrated in a modification developed by Bach.[19] For example, reaction of dithioacetal **23** and diene **24** gave ketone **25** as a mixture (4:1) of diastereoisomers (Scheme 4). Each diastereoisomer underwent a stereoselective rearrangement mediated by mercury(II) trifluoroacetate to give the corresponding mixture of 1,3-diketones **26** which was transformed into spirodiketone **28** by aromatization of ring E.



Scheme 4 *Reagents and conditions:* (a) $BF_3 \cdot Et_2O$, CH_2Cl_2, -60 to -40 °C, 1.5 h, 52%; (b) $Hg(O_2CCF_3)_2$, PhH, 0 °C, 1 min, 81%; (c) Br_2, AcOH, rt, 15 min, 98 %; (d) NaH, THF, reflux, 75 min, 71% (reference 19a)

The same strategy was applied in the elaboration of a more advanced model of fredericamycin A (Scheme 5). 1,2-Bis(trimethylsiloxy)cyclobutene **29** and dithioacetal **23** were coupled together, and the mercury-induced rearrangement of compound **30** gave the corresponding spirodiketone **31**. A double bond was then introduced in ring D in preparation for the Diels-Alder reaction between diene **34** and dienophile **32**. The cycloaddition adduct **35** was finally converted into hydroquinone **36**, having the proper

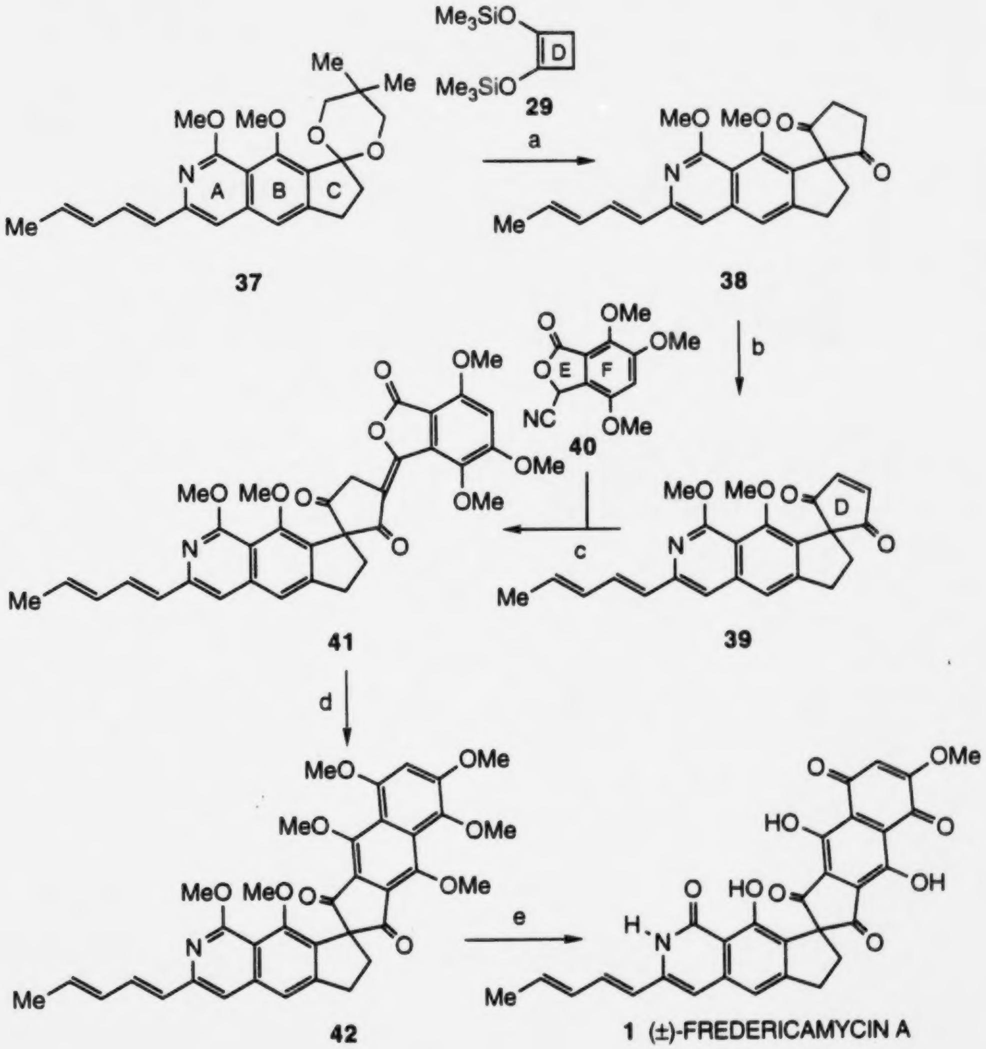


Scheme 5 *Reagents and conditions:* (a) 3 equiv of $BF_3{\cdot}Et_2O$, CH_2Cl_2, -60 °C, addition of **29**, -40 °C, 1 h, 59%; (b) $HgCl_2$, PhH, 80 °C, 15 min, 94%; (c) Br_2, AcOH, rt, 1 h, 68%; (d) *n*-BuLi, THF, -78 °C, 30 min, 1.2 equiv of Me_3SiCl; warm rt, 5 min; cool -78 °C, 1.1 equiv of **32**; warm rt, 6 h; (e) flash chromatography, 62% (reference 19c)

oxygen substitution of the fredericamycin A northern moiety, but lacking the required oxidation level.

The Kuwajima reaction was also used by Parker[14a] and Pandey[20] in the construction of simpler models of fredericamycin A.

Finally, Julia[21] completed a total synthesis of racemic fredericamycin A using this method (Scheme 6). In this linear approach, acetal **37**, already having the pentadienyl tail,



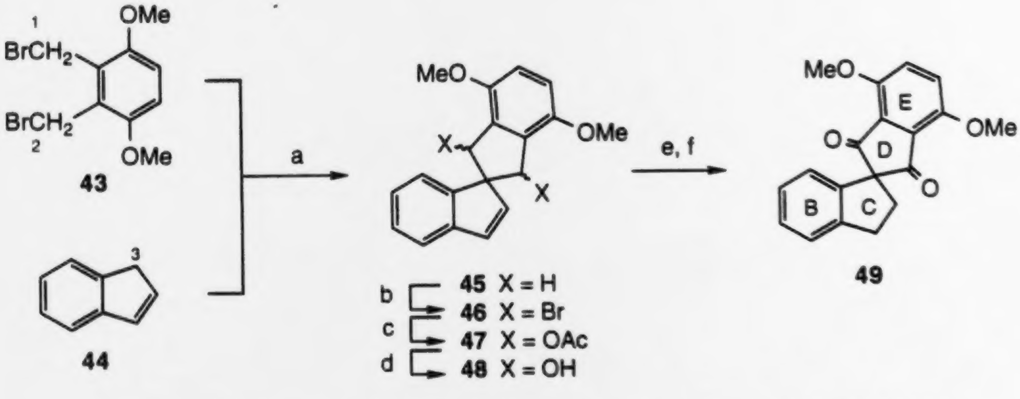
Scheme 6 *Reagents and conditions:* (a) 3 equiv of 1,2-bis(trimethylsilyloxy)-cyclobutene, 10 equiv of $BF_3 \cdot Et_2O$, CH_2Cl_2, -78 °C, 1 h, rt, 4 h, 33%; (b) DBU, $C_6H_5NMe_3Br \cdot Br_2$, THF, rt, 4 h, 33%; (c) 1.2 equiv of **40**, 1.2 equiv of LDA, THF, -78 °C, 63%; (d) NaH, MeONa, THF, -25 °C, 10 min, 95%; (e) Me_3SiCl, NaI, CH_2Cl_2/CH_3CN (1:1) (f) 6 equiv of BBr_3, CH_2Cl_2, -78 °C, 1 h, rt, 2 h, then air, $CHCl_3$, 48 h, 30% (two steps) (reference 21)

was reacted with 1,2-bis(trimethylsiloxy)cyclobutene **29** to give diketone **38** in modest yield. A double bond was introduced in ring D (**38**→**39**), and 1,4-addition of the carbanion derived from cyano compound **40** (an isomer of **33**, used previously in a Diels-Alder reaction, Scheme 5) to diketone **39** gave the coupling compound **41**. Cyclization of the E ring occurred upon treatment of lactone **41** with sodium hydride and sodium methoxide. Finally, boron tribromide cleaved selectively six of the seven methyl ethers, and air oxidation produced racemic fredericamycin A **1**. This last step, which is so crucial in an all-methyl protection strategy, is based on the prior synthesis (see below) carried out in this laboratory.

Indenyl Anion

Some synthetic approaches reported the use of the indenyl anion (ring B-C).[15,22,23] Also, a few methodologies were developed using this nucleophile for the construction of the spiro center.

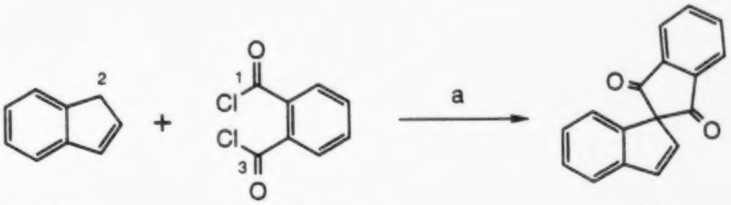
In one of these methods, Julia[24] developed a two phase reaction involving the alkylation of indene (Scheme 7). Treatment of indene **44** and 1,2-bisbromomethyl benzene



Scheme 7 *Reagents and conditions:* (a) 50% aq NaOH, THF, Me_3NBnBr, 50 °C, 4 h, 34%; (b) NBS, CCl_4; (c) AcOAg, AcOH, reflux, 4 h; (d) $LiAlH_4$, Et_2O, rt; (e) 5% Pd/C, 50 bar H_2, Et_2O; (f) PCC, CH_2Cl_2, rt, 20% (from **45**) (reference 24)

43 with sodium hydroxide and a phase transfer catalyst in a two solvent system gave tetracyclic compound **45** which was converted into spirodiketone **49** by a rather lengthy sequence of functional group transformations.

A more efficient use of this strategy was reported by Ayyangar.[25] Acylation of the anion derived from indenyl **44** with phthaloyl chloride **50** gave directly spirodiketone **51**, but again the yields are quite modest (Scheme 8).

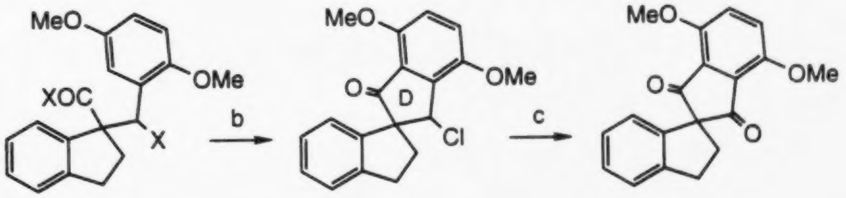


44 **50** **51**

Scheme 8 *Reagents and conditions:* (a) 2 equiv of NaH, *n*-Bu_4NBr, PhH, rt, 30% (reference 25)

Intramolecular Friedel-Crafts Acylations

Julia[21,26] relied on an intramolecular Friedel-Crafts acylation for the construction of ring D. The direct route[26] gave very poor yields, therefore a stepwise approach was designed (Scheme 9). Treatment of acyl chloride **53** with aluminium chloride gave the



a **52** X = OH → **53** X = Cl

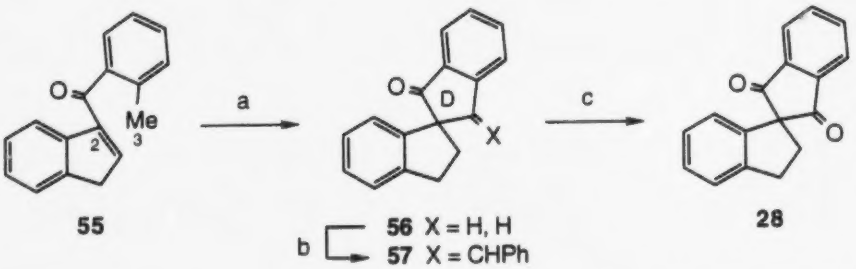
54

49

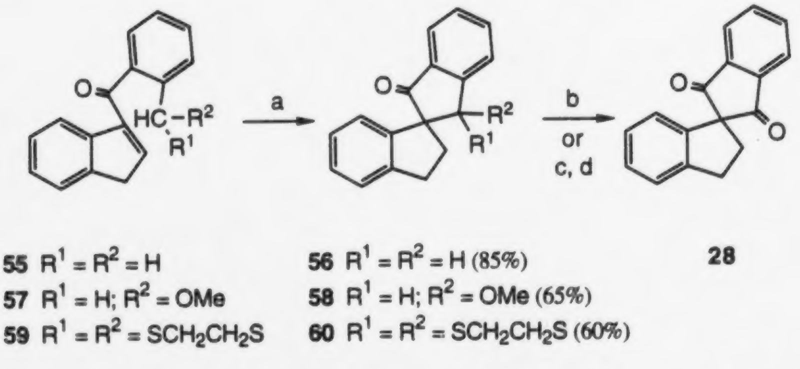
Scheme 9 *Reagents and conditions:* (a) 2 equiv of $SOCl_2$, DMF, CH_2Cl_2; (b) $AlCl_3$, CH_2Cl_2, 0 °C, 53% (over two steps); (c) DMSO, $NaHCO_3$, 150 °C, 90% (reference 21) ketone **54** which was converted smoothly into diketone **49**. Although this stepwise route gave higher yields, the intramolecular Friedel-Crafts failed in the complex series leading to the synthesis of fredericamycin A.

Photochemical Induced Cyclization

Mehta[22] reported a photo-induced rearrangement for the formation of ring D of fredericamycin A (Scheme 10). Irradiation of enone **55** led to the formation of ketone **56** which was converted into spirodiketone **28** through benzylidene **57**. The proposed mechanism of this rearrangement involves a radical abstraction from the methyl group and subsequent recombination of both radicals at position 2 and 3. An investigation of the



Scheme 10 *Reagents and conditions:* (a) *hv*, PhH, 65%; (b) $(Me_3Si)_2NLi$, PhCHO, THF, -45 °C; (c) RuO_2-$NaIO_4$, aq CH_3CN, CCl_4, 50% (over two steps) (reference 22)

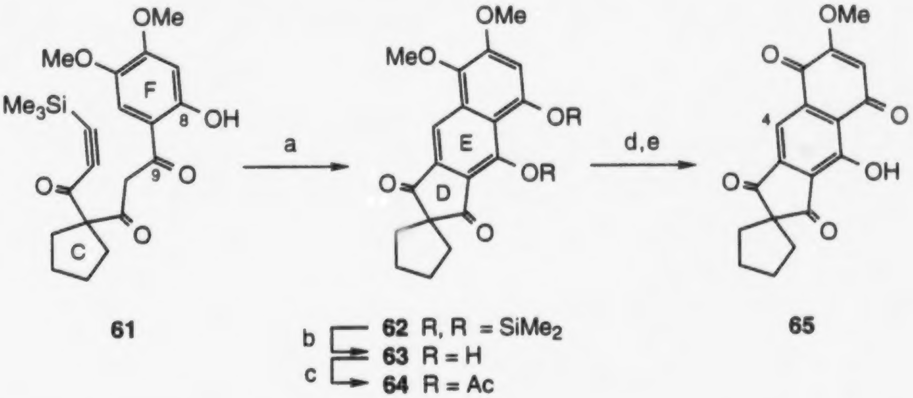


Scheme 11 *Reagents and conditions:* (a) *hv*, PhH; (b) 4 equiv of CAN, H_2O/CH_3CN (1:3), rt, 3 min (reference 23b), 56%; (c) Me_3SiI, 50%; (d) PCC, 82% (reference 23b)

effect of radical stabilizing substituents at the abstraction site was reported[23] (Scheme 11). Surprisingly, the best yields of spirocyclization were obtained in the unsubstituted series. Nevertheless, each ketone could be converted into spirodiketone **28**.[27]

Intramolecular Diels-Alder Reaction

In this most unusual approach, Terashima[28] and Kita[29] used an intramolecular Diels-Alder reaction to construct simultaneously both ring D and ring E of fredericamycin A (Scheme 12). In Kita's example, the oxygens at position 8 and 9 are protected as a cyclic silicon ether (**61**→**62**) prior to the intramolecular Diels-Alder reaction. The tetracyclic product **62** was converted into spirodiketone **65**, which lacks the oxygen at position 4 of fredericamycin A.

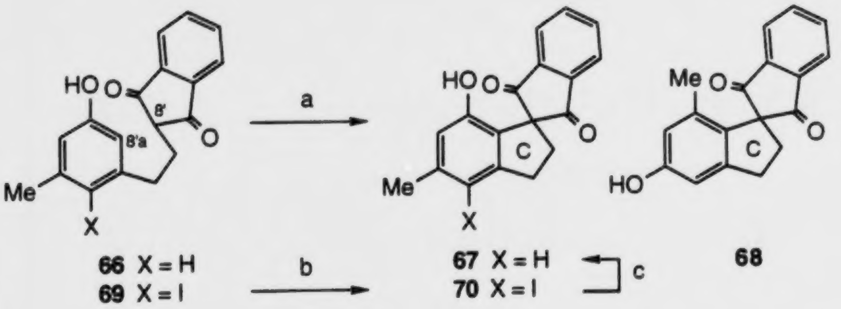


Scheme 12 *Reagents and conditions:* (a) Me_2SiCl_2, Et_3N, chloranil, PhH, 130–150 °C, sealed tube; (b) MeOH, reflux; (c) Ac_2O, pyridine, 77% (from **61**); TFA, H_2O, reflux; (e) 10 equiv of phenyliodosyl bistrifluoroacetate, CH_3CN, H_2O, rt, overnight, 98% (over two steps) (reference 29)

Construction of Ring C of the Fredericamycin A Spiro Center

Ferricyanide And Manganese(III) Acetate Oxidations

An oxidation reaction, promoting the intramolecular coupling of a phenoxy radical (8'a) and enoxy radical (8') was designed by Kende[30] to form ring C (Scheme 13). When phenol **66** (X = H) was treated with potassium hexacyanoferrate(II), undesired spirodiketone **68** was obtained as the major product (67%), the result of reaction with the wrong regioselectivity. Introduction of a halogen substituent at the *para*-position (**69**, X = I) furnished the desired spirodiketone **70** (X = I) in an improved yield, and the superfluous iodine was then removed photochemically.

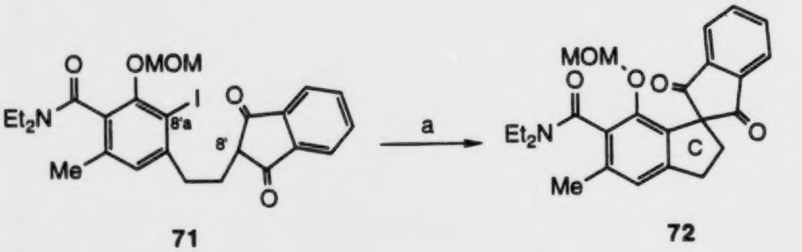


Scheme 13 *Reagents and conditions:* (a) 0.5 M Na_2CO_3, 6 equiv of 0.5 M $K_3Fe(CN)_6$, 0 °C, 10 min, 8% ; (b) 0.5 M Na_2CO_3, 6 equiv of 0.5 M $K_3Fe(CN)_6$, 0 °C, 10 min, 46%; (c) NaOAc, *i*-PrOH, *hv*, 60-70 °C, 10 h, 59% (reference 30)

Manganese(III) acetate[31] was also used to accomplish a similar radical coupling, in comparable yields. In this method, the introduction of an extra halogen was not required.

Palladium(0)-Catalyzed Cyclization: Displacement of Aromatic Halides

A new general method, which relies on palladium catalysis to induce cyclization by intramolecular displacement of aromatic halides, was introduced by Ciufolini[32] for the construction of the carbon-carbon bond between positions 8' and 8'a (Scheme 14).

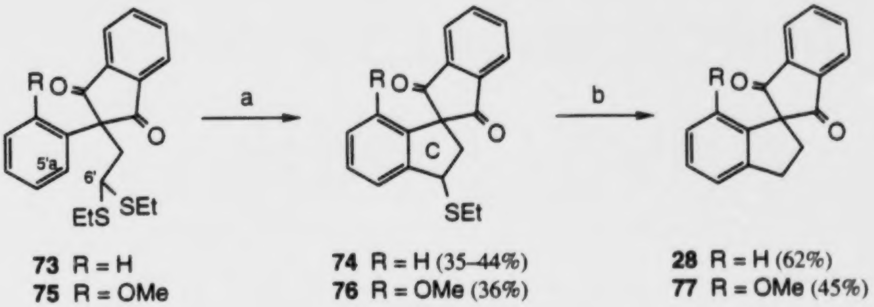


Scheme 14 *Reagents and conditions:* (a) NaH, $Pd(PPh_3)_4$, DMF, 135 °C, 30 min, 76% (reference 32b)

Iodide **71** was treated with sodium hydride in the presence of tetrakis(triphenylphosphine)-palladium(0) to give the desired spirodiketone **72** in good yield.

Intramolecular Friedel-Crafts Type Reaction

A different use of an intramolecular Friedel-Crafts reaction was described by



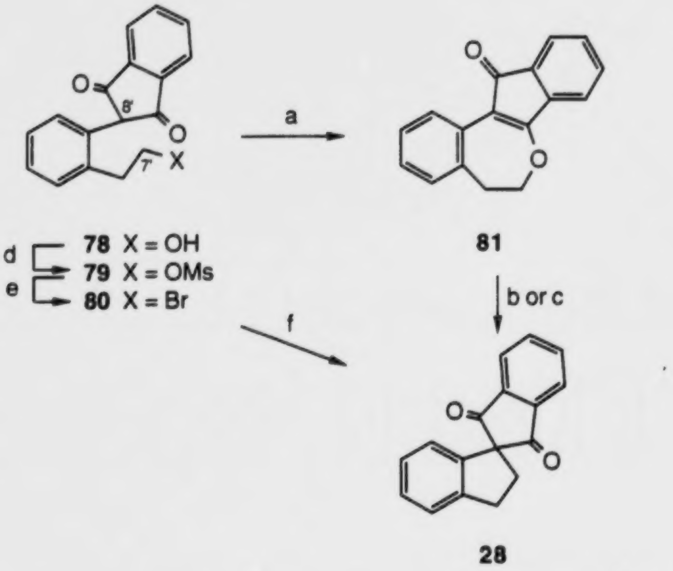
Scheme 15 *Reagents and conditions:* (a) $AgClO_4$ or $AgBF_4$ or $AlCl_3$, CH_3NO_2, heat; (b) Raney nickel (reference 33)

Braun[33] (Scheme 15). Ring C of fredericamycin A was formed from either thioacetals **73** or **75** on treatment with a Lewis acid. Spirodiketones **74** and **76** were each desulfurized.

Rearrangement of Oxepine

In the first[34] approach ever reported in the literature for the synthesis of fredericamycin A, a methodology was developed for joining carbon 7' and carbon 8' (Scheme 16). Treatment of alcohol **78** with catalytic amount of acid gave oxepine **81** which was rearranged by thermolysis into diketone[35] **28** in acceptable yields.

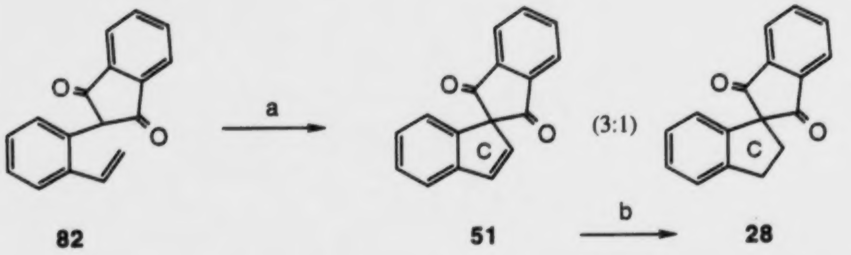
Only much later, Rama Rao[36] reported a similar conversion obtained by chemical means. Spirodiketone **28** was also obtained from oxepine **81** by treatment with trimethylsilyl iodide. Rama Rao revived his initial approach based on this later information. Alcohol **78** was converted into the desired spirodiketone **28** through its mesylate **79** and bromide **80**.



Scheme 16 *Reagents and conditions:* (a) cat. *p*-TsOH, CH_2Cl_2, 95%; (b) 290-300 °C, 5 h, 40% (reference 34); (c) Me_3SiCl, NaI, $CHCl_3$, rt, 20 h, 35%; (d) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 h, 91%; (e) LiBr, THF, reflux, 45 min, 90%; (f) Me_3SiCl, NaI, CCl_4, rt, 15 h, 45% (reference 36)

Palladium(II)-Mediated Cyclization

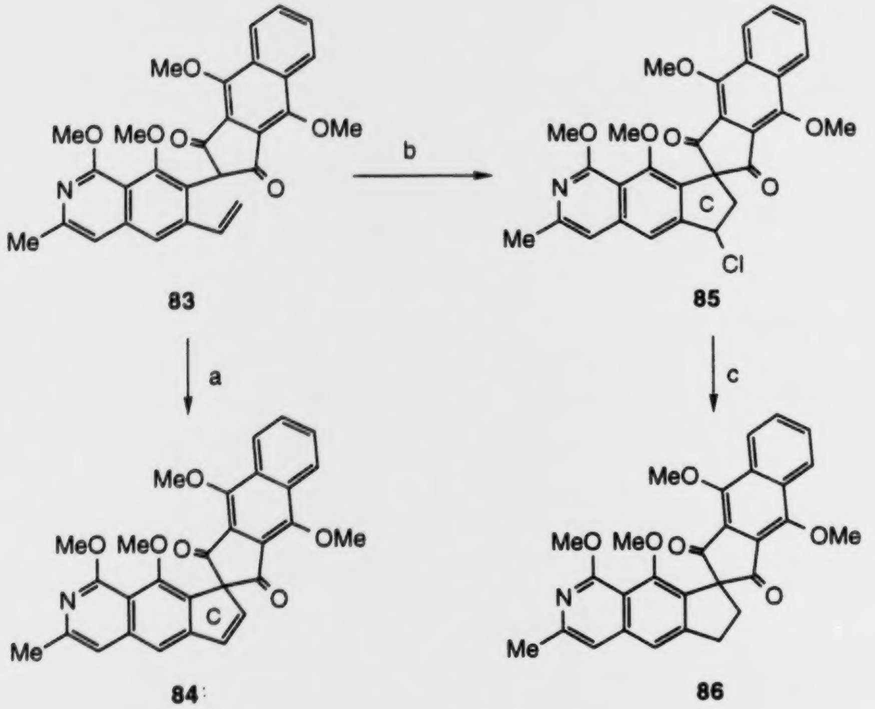
A more convenient approach was introduced by Rama Rao[36,37] using palladium(II)-mediated cyclization for the formation of ring C (Scheme 17). Diketone **82** was converted into the corresponding sodium enolate which in the presence of palladium(II) acetate gave both cyclization products **51** and **28**. The former compound was hydrogenated to furnish cleanly the desired spirodiketone **28**.



Scheme 17 *Reagents and conditions:* (a) NaH, DMF, rt, 15 min, then $Pd(OAc)_2$, rt, 5 h, 50% (overall); (b) H_2, 10% Pd/C, EtOH, rt, 5 h, 90% (reference 36)

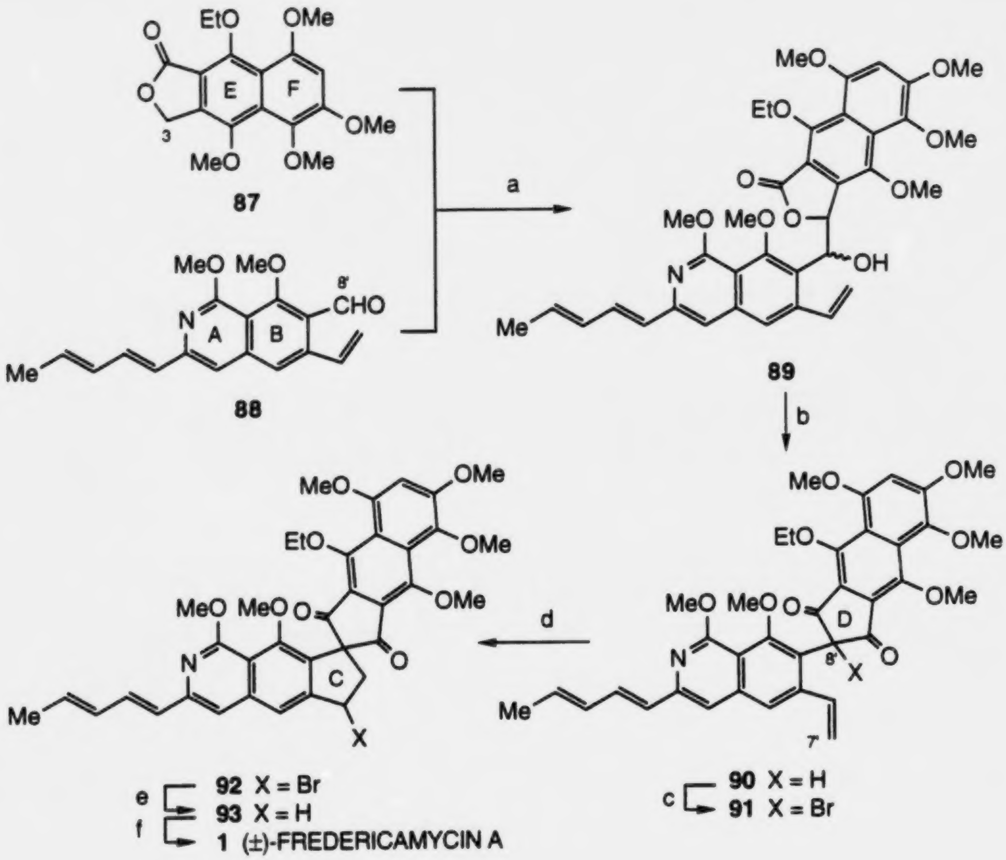
5-Endo-trig-Radical Cyclization

Rama Rao[38] also reported a very mild and general approach for constructing the spiro[4.4]nonane utilizing manganese(III) based oxidative free radical cyclization (Scheme 18). Diketone **83** was cleanly cyclized to spirodiketone **84** which had an additional double bond in ring C. Addition of chloroform (1 equivalent) provided a source of chlorine atoms, and led to the formation of chloride **85**, which was easily dehalogenated by hydrogenolysis (**85→86**).



Scheme 18 *Reagents and conditions:* (a) 1 equiv of $Mn(OAc)_3$, 1 equiv of $Cu(OAc)_2$, AcOH, rt, 30 min, 72%; (b) 1 equiv of $Mn(OAc)_3$, 1 equiv of $Cu(OAc)_2$, 1 equiv of $CHCl_3$, rt, 30 min, (c) Pd/C, H_2, MeOH, rt, 12 h, 86% (reference 38)

The preceding result suggested the use of a more conventional method of radical cyclization. With this methodology, Rama Rao[39] completed the total synthesis of racemic fredericamycin A (Scheme 19). In this convergent synthesis, addition of the anion (at C-3) of lactone **87** to aldehyde **88** (8') gave a mixture of alcohols which was rearranged into

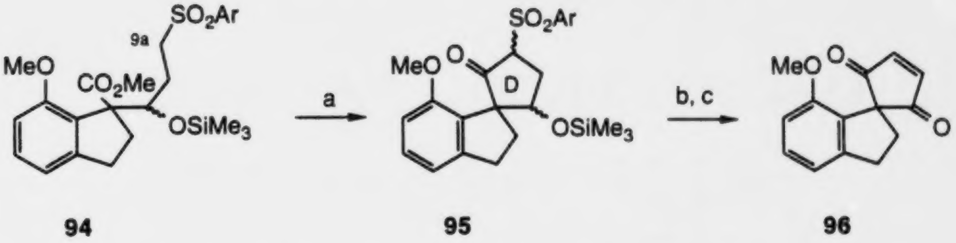


Scheme 19 *Reagents and conditions:* (a) LDA, HMPA, -78 °C, 3 h, 54%; (b) MeONa, MeOH, ethyl propionate, reflux, 1.5 h, 58%; (c) $CuBr_2$, $Mn(OAc)_3$, rt, 15 min, 80%; (d) 1 equiv of Ph_3SnH, 0.03 equiv of AIBN, benzene, 50 °C, slow addition 12 h; (e) 1.1 equiv of Ph_3SnH, benzene, 2 h, reflux, 55%; (f) BBr_3, CH_2Cl_2, 30 min, -78 °C, 10 min, 0 °C, no yield reported (reference 39b)

diketone **90**. A homolysable group was then introduced (**90→91**), and the radical stannane-mediated halogen transfer gave the cyclized product **92**. This was debrominated by the addition of more tin hydride. The synthesis of fredericamycin A **1** was completed with the removal of six of the seven protective ethers, again by analogy with the last steps of the U of A synthesis (see below).

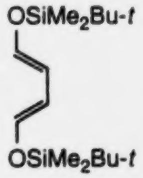
Our Approaches to the Synthesis of Fredericamycin A

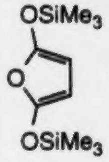
The strategies developed by our group tackled the construction of a carbon-carbon bond in ring D of the spiro center of the antitumor agent. The first approach[40] relied on a Dieckmann-type reaction to form the 5-membered ring (Scheme 20). Sulfone **94** was deprotonated with a strong base (position 9a), and the spiroketone **95** was obtained. Oxidation with Jones' reagent followed by purification on silica gel furnished the desired spirodiketone **96** in excellent yield. Our plan included a Diels-Alder reaction for the construction of ring E, but unfortunately this dienophile **96** reacted poorly[41] with either dienes **97** or **98**. For the combination dienophile **96** and diene **97**, high pressure (*ca.* 20 kbar) and long reaction periods (55 h) were required in order to obtain satisfactory (48%) yields of the cycloaddition adduct.



Scheme 20 *Reagents and conditions:* (a) 2.5 equiv of LDA, THF, -78 °C, 1 h; 0 °C, 1 h, 85% (mixture of isomers); (b) $H_2Cr_2O_7$, acetone, H_2O, 0 °C; (c) silica gel chromatography, 88% (reference 40)

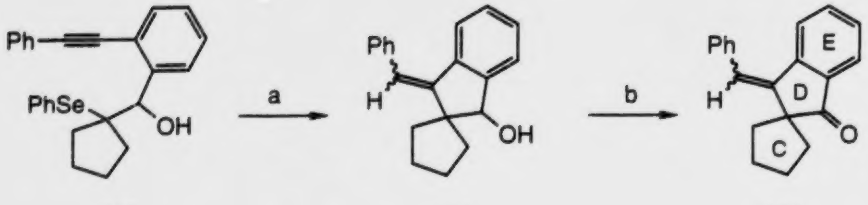
97





98

Many reviews[42] described the efficient use of radical cyclization in the formation of 5-membered carbon rings. By extension, a new methodology based on this reaction was developed for the construction of the congested center found in fredericamycin A (Scheme 21). In this simplified model, treatment of selenide **99** with triphenyltin hydride induced

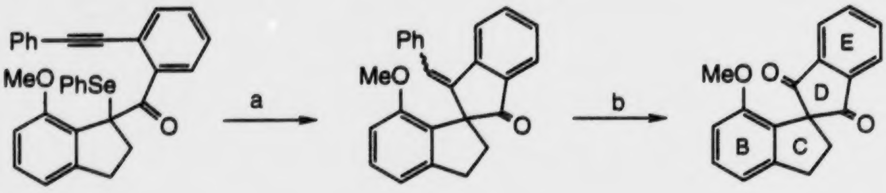


99 **100** **101**

Scheme 21 *Reagents and conditions:* (a) 1.4 equiv of Ph_3SnH, 0.2 equiv of AIBN, PhH, reflux, slow addition 7 h + 2 h, 91%; (b) PCC, CH_2Cl_2, rt, 1 h, 83% (reference 43)

radical cyclization and furnished alcohol **100**.[43] The hydroxyl group was oxidized with pyridinium chlorochromate to give ketone **101**.

A more elaborate model[40] was designed to include the ring B–E framework of fredericamycin A (Scheme 22). Indeed, the radical cyclization of selenide **102** proceeded

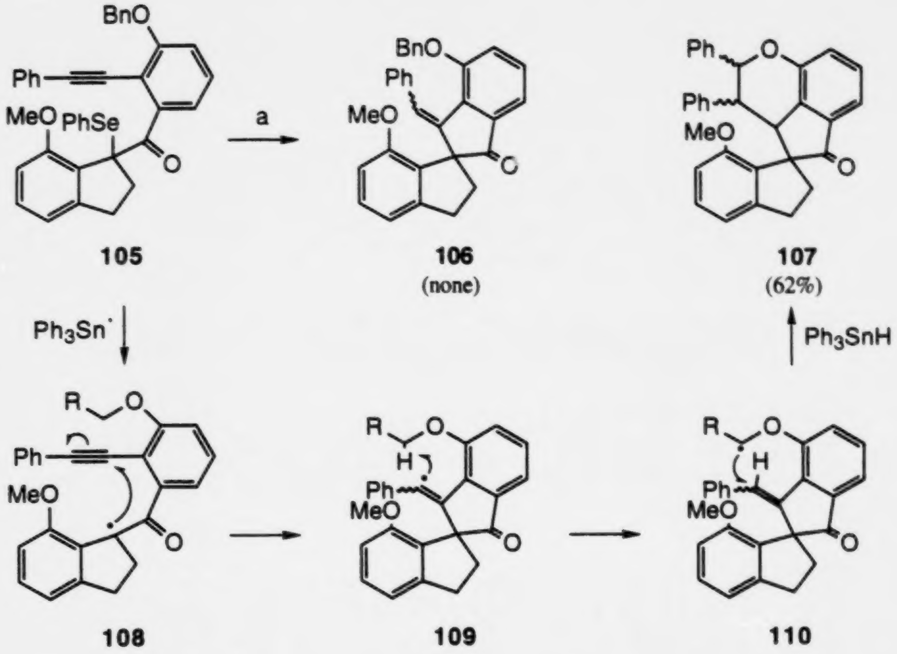


102 **103** **104**

Scheme 22 *Reagents and conditions:* (a) Ph_3SnH, AIBN, PhH, reflux, slow addition 7 h + 2 h, 85%; (b) O_3, $CHCl_3$, -60 °C; Me_2S, rt, 36 h, 84% (reference 40)

smoothly (85%), and the resulting ketone **103** was converted into spirodiketone **104**.

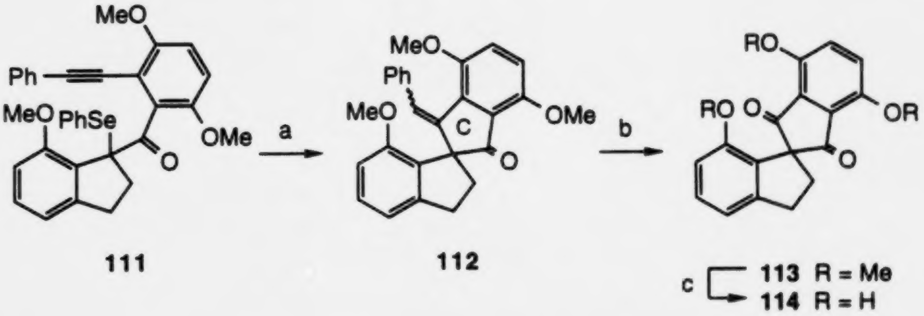
Introduction of one oxygen substituent in ring E was examined in the next example (Scheme 23). The cyclization of selenide **105** gave none of the desired ketone **106**. Instead, a product **107** was isolated in good yield, and the rationale for its formation became obvious. Homolytic cleavage of the selenide **105** gave radical **108** (R = Ph) which added in a 5-*exo-dig* manner, as expected, to the acetylene. The resulting vinyl radical **109** (R = Ph) abstracted a benzylic hydrogen (1,6-hydrogen transfer) to give stabilized radical **110** (R = Ph), which then added to the resulting olefin in a 6-*endo-trig*



Scheme 23 *Reagents and conditions:* (a) 1,4 equiv of Ph_3SnH, AIBN, PhH, reflux (reference 40)

fashion to give pentacyclic compound **107** after reduction with the stannane reagent. This product **107** was of no use for the synthesis of fredericamycin A.

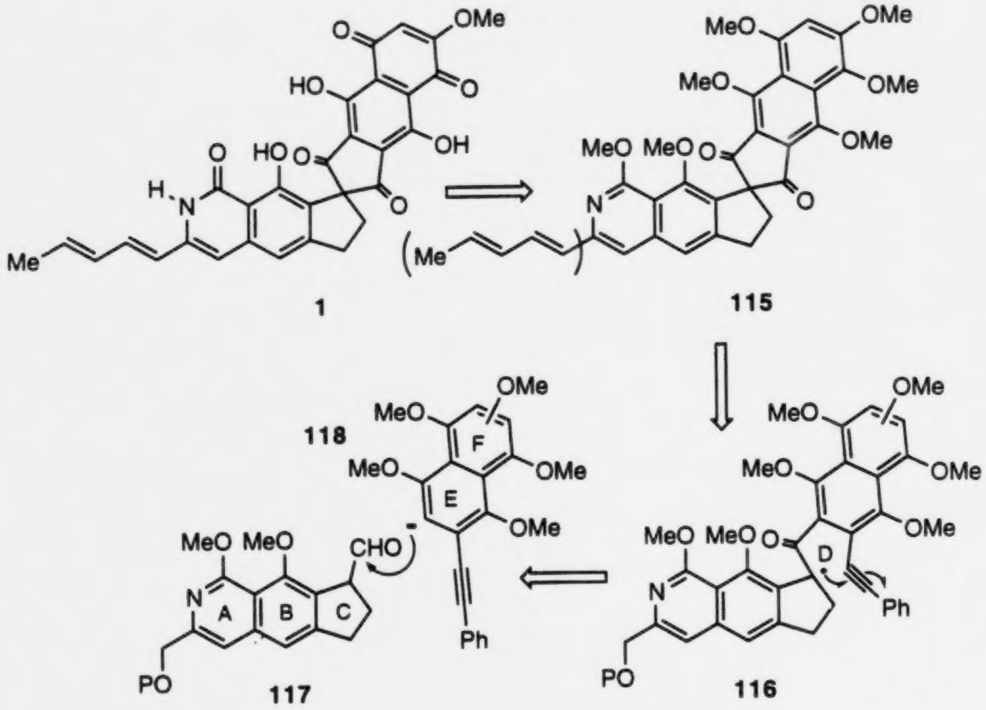
A more elaborate model[44] was constructed, with the two *para*-related oxygens of ring E (position 4 and 9) protected as more resistant methyl ethers (Scheme 24). The



Scheme 24 *Reagents and conditions:* (a) 1.7 equiv of Ph_3SnH, AIBN, benzene, reflux, 12 h, 79%; (b) O_3, MeOH, -78 °C; $(MeO)_3P$, rt, overnight, 61%; (c) 9 equiv of BBr_3, CH_2Cl_2, addition - 78 °C, rt, overnight, 85% (reference 44)

radical cyclization of selenide **111** gave spiroketone **112** in good yield, with no evidence of the formation of rearranged compound. The exocyclic double bond was cleaved, and the hydroxyl groups were liberated (**112→113→114**).

From the experience gained in these model series, a synthetic plan for the total synthesis of racemic fredericamycin A was formulated (Scheme 25). The natural product **1**



Scheme 25

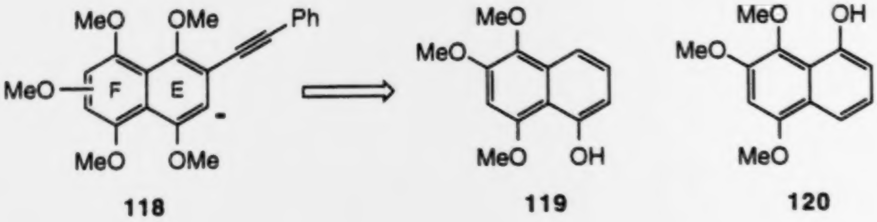
would come from a fully protected intermediate **115** at which stage the pentadienyl tail (section of the molecule in brackets) would be introduced. Radical spirocyclization would enable us to construct ring D of fredericamycin (**115⇒116**). Our convergent approach, involving the assembly of advanced intermediate **116** by the coupling of two subunits (**116⇒117 + 118**), would be an attractive route.

When I joined the group involved in the synthesis of fredericamycin A, a synthesis of an advanced intermediate of the southern moiety had already been published.[45] Therefore, more attention was required for the synthesis of the EF ring portion.

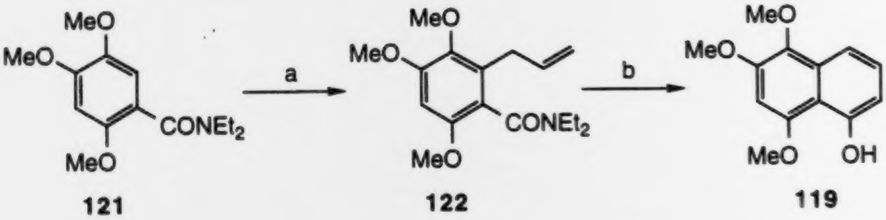
II DISCUSSION

A Diels-Alder Approach to EF Rings

In the course of the total synthesis of a complex natural compound, early intermediates are required in large quantities. Based on our plan for the synthesis of rings EF (**118**) of fredericamycin A (Scheme 26), an efficient synthesis of either trimethoxynaphthol **119** or its regioisomer **120** was needed. The early synthesis[46] of isomer **120** relied on the methodology of directed *ortho*-lithiation from the diethylamide functional group to introduce the three carbon segment forming ring E (Scheme 27).

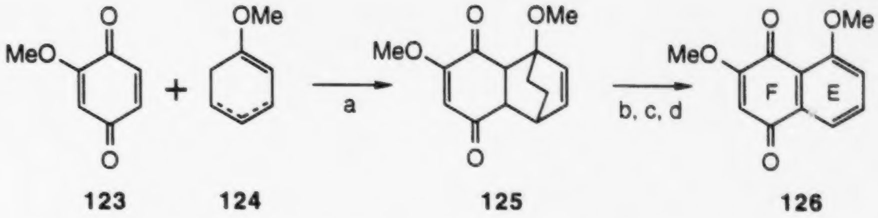


Scheme 26



Scheme 27 *Reagents and conditions:* (a) *s*-BuLi, TMEDA; $MgBr_2 \cdot Et_2O$, 3-bromopropene, THF, addition -78 °C, rt, 20 h, 71%; (b) LDA, THF, addition -78 °C, rt, 20 h, 86% (reference 46)

A Diels-Alder approach[47] appeared to be a suitable alternative for construction of the naphthol. Giles[48] reported the cycloaddition 2-methoxy-1,4-benzoquinone **123** and a mixture of 1-methoxycyclohexa-1,3 and 1,4-diene **124** (Scheme 28). The Diels-Alder

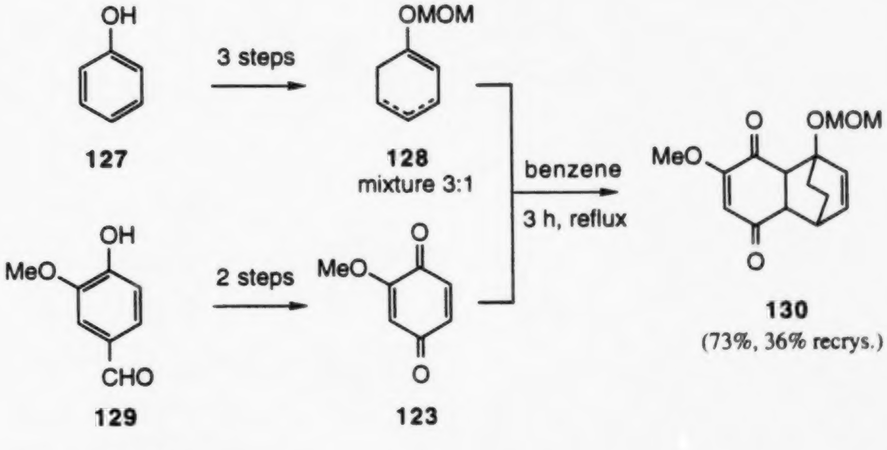


Scheme 28 *Reagents and conditions:* (a) benzene, 80 °C, 1.5 h, 60%; (b) *t*-BuOK, THF; (c) Ag_2O, Et_2O, rt, 3.5 h, 100% (over two steps); (d) 120 °C, 8 mm Hg, 98% (reference 48a)

adduct **125** was also converted into quinone **126** which possesses the desired oxygen substitution for the synthesis of isomer **120**.

For our synthesis of ring EF using this approach, we selected the methoxymethyl ether as protecting group for the hydroxyl of the diene to enable selective deprotection of the future E ring. We planned to convert a quinone, having the ring E hydroxyl group protected as a methoxymethyl ether (instead of the methoxy ether of quinone **126**), into the fully protected naphthalene ring in two simple chemical steps: reduction of the ring F quinone, and protection of the hydroquinone as its methyl ethers.

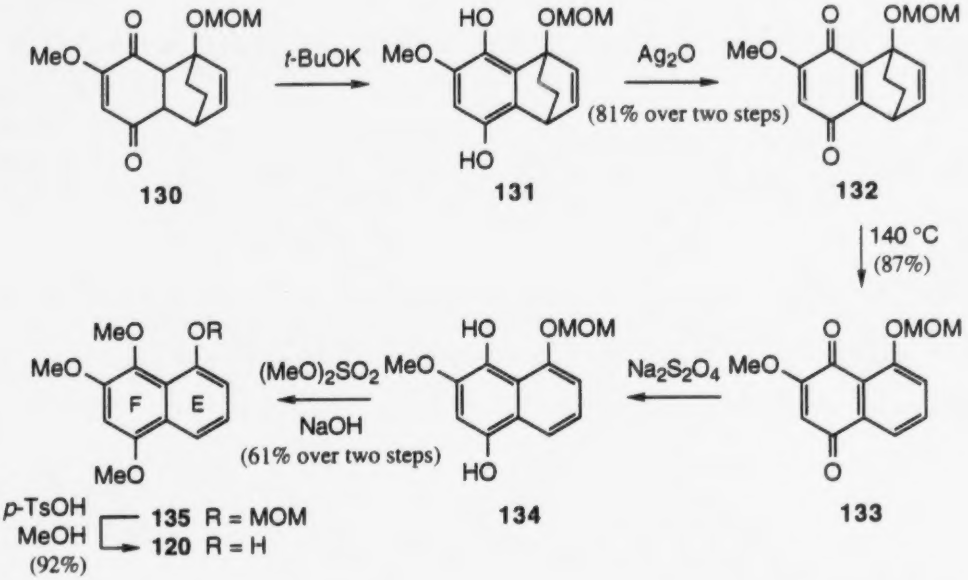
The required diene **128** was easily prepared from phenol[49] **127** as a mixture (*ca.* 3:1) of the 1,3- and -1,4-dienes, and the other component was made by converting vanillin into 2-methoxy-1,4-benzoquinone **123** by known methodology[50] (Scheme 29).



Scheme 29

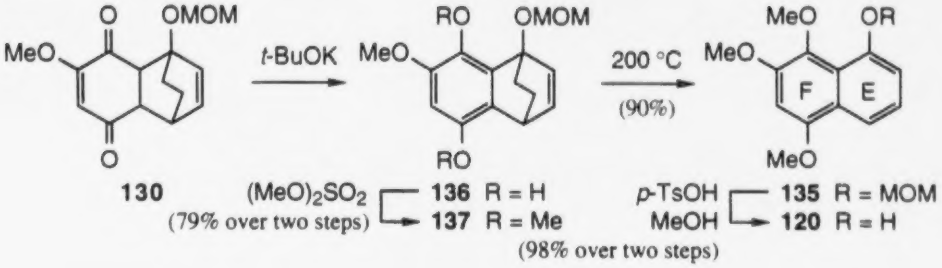
The Diels-Alder adduct[51] **130** was produced by heating a benzene solution of the dienes **128** and the dienophile **123**. The fact that only a single isomer was isolated suggested that the regiochemistry of our product was identical to adduct **125** (Scheme 28).

The Diels-Alder adduct **130** was converted by use of Giles' method[48] into quinone **132** (Scheme 30). The bridge segment was then expelled by heating a solution of quinone **132** in dry xylenes at 140°C. Then quinone **133** was reduced with sodium hydrosulfite, the phenolic hydroxyl groups were protected as methyl ethers, and the methoxymethyl ether was cleaved to give the desired isomer **120**.



Scheme 30

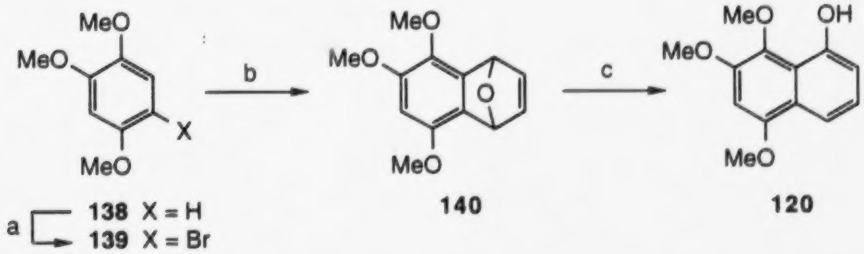
This cycloaddition route was further simplified. Treatment of the Diels-Alder adduct **130** with potassium *tert*-butoxide, as previously performed, followed by the earlier protection of the two phenolic hydroxyl groups as methyl ethers, gave compound **137** (Scheme 31). Ethylene was expelled at this stage by heating a solution of the trimethoxy compound **137** in dry methyl benzoate under reflux (*ca*. 200 °C). Clearly, elimination of ethylene from this substrate required more thermal energy than in the



Scheme 31

preceding example (**132**→**133**, Scheme 30). Some deprotection of the methoxymethyl ether was occasionally observed [tlc, silica]. In those experiments, the crude product was treated with methanol in the presence of a catalytic amount of acid to give a material (**120**), identical to that obtained by our previous longer route. This shorter approach eliminates the unnecessary oxidation (**131**→**132**) and the reductions steps (**133**→**134**) of the original Diels-Alder route (Scheme 30).

Meanwhile, a shorter and more efficient synthesis[46] of isomer **120** was developed in this laboratory. The new approach was based on the cycloaddition of furan and a benzyne intermediate obtained by the action of a strong base on bromide **139** (Scheme 32). By this route, trimethoxynaphthalenol **120** was available in multi-gram quantities (*ca.* 50 g), and so it became unnecessary to scale up the Diels-Alder approach.

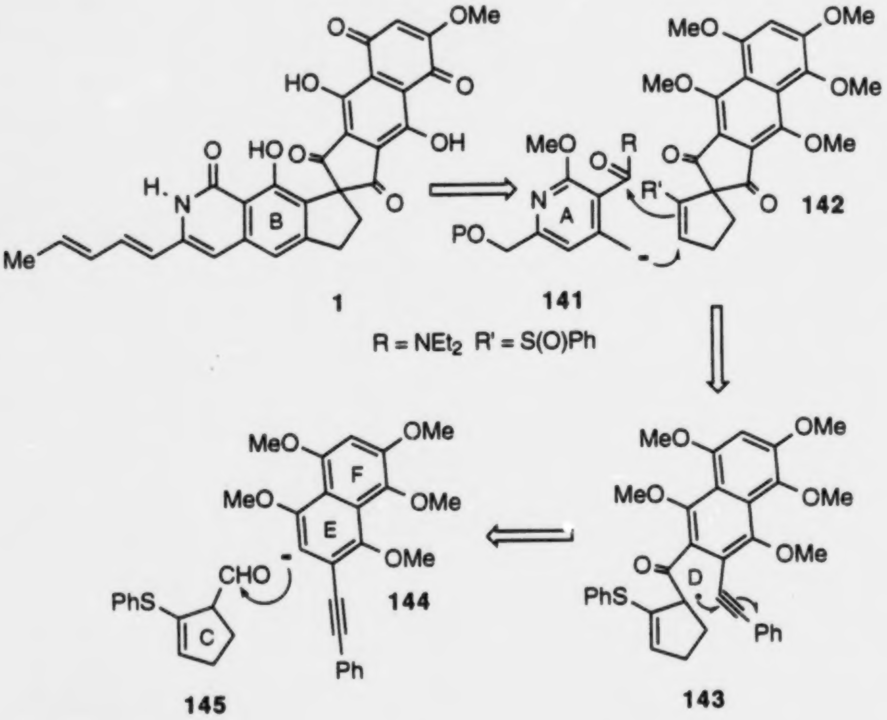


Scheme 32 *Reagents and conditions:* (a) Br$_2$, CHCl$_3$, 0 °C, slow addition 4 h, 98%; (b) LDA, furan, THF, -78 °C, 4 h, rt, overnight; (c) HClO$_4$, 0 °C, addition, rt, 1.25 h, 95% (over two steps) (reference 46)

The Linear Approaches

Our convergent approach to the synthesis of fredericamycin A relied on the assembly of the bottom piece **117** and the top piece **118** for the formation of intermediate **116** (Introduction, Scheme 25). At the time when the Diels-Alder approach to the construction of rings EF was terminated, the coupling reaction (**117** + **118**→**116**) was providing only low yields. To bypass this problem, two linear approaches for the synthesis of fredericamycin A were planned.

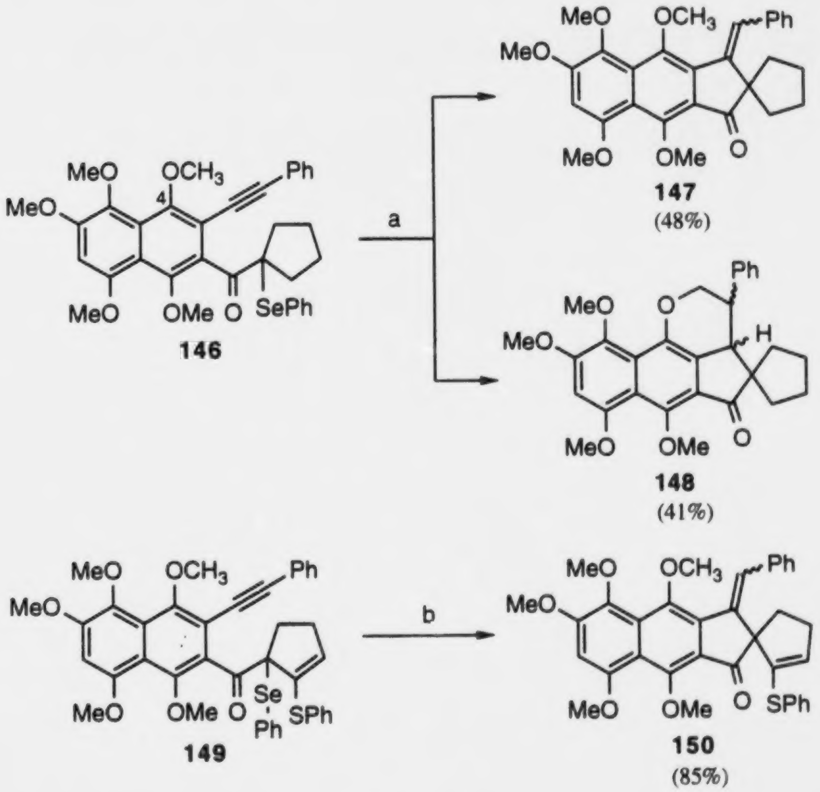
The first linear approach (Scheme 33) was inspired by the strategy used in the construction of our southern portion of fredericamycin A.[45] Conjugate addition of anion **141** to unsaturated sulfoxide **142** would make the connection between ring A and the



Scheme 33

the main structure **142** and, in principle, could form ring B simultaneously. Ring D (*cf.* **143**) would be constructed using a radical spirocyclization, for which the precursor would be assembled by a coupling reaction between anion **144** and aldehyde **145**.[52]

Also, two new results[46,53] of radical spirocyclization in advanced models of fredericamycin A became available in the group (Scheme 34). When a solution of selenide



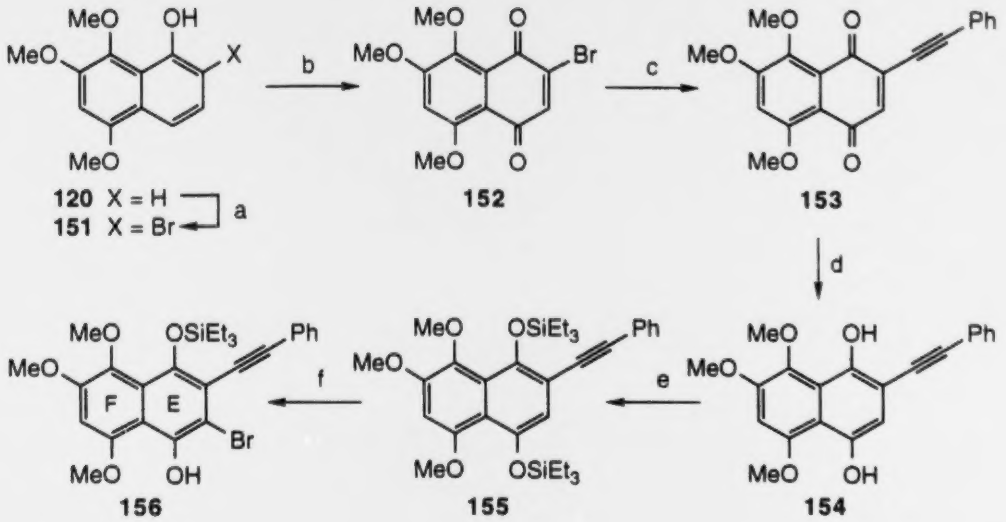
Scheme 34 *Reagents and conditions:* (a) Ph_3SnH, AIBN, benzene, 80 °C, overnight (reference 46); (b) Ph_3SnH, AIBN, benzene, 80 °C, overnight (reference 53)

146 was heated at 80 °C in the presence of triphenyltin hydride and catalytic amounts of AIBN, rearrangement compound **148** (see mechanism of formation in Introduction, Scheme 23, R = H) was isolated in 41% yield along with 48% of the desired compound **147**. This result was rather disappointing; in previous examples[40, 44] of radical spirocyclization (Introduction Scheme 22 and Scheme 24), the hydrogen atoms of the methyl ether (C-4) resisted abstraction by the vinyl radical. Similar behavior of the methyl ether in the series leading to the total synthesis of fredericamycin A would be disastrous, since half of the material would be lost at this advanced stage.

On the other hand, radical spirocyclization of selenide **149** under our standard conditions gave the spiro compound **150** in a higher yield. We cannot offer any explanation for the higher yield in the later series. Nevertheless, the second model appeared suitable for studying the behavior of various protective groups on ring E during the radical spirocyclization. By utilizing a protective group other than a methyl ether, we might achieve selective deprotection of ring E later in the synthesis of fredericamycin A. Benzyl ethers, which may be selectively removed by hydrogenolysis of the benzylic C–O bonds, were chosen, despite the earlier observation that activated benzylic hydrogens were easily abstracted (Introduction, Scheme 23). We were hopeful that the more favorable cyclization of compounds such as selenide **149** would outweigh the abstraction problem.

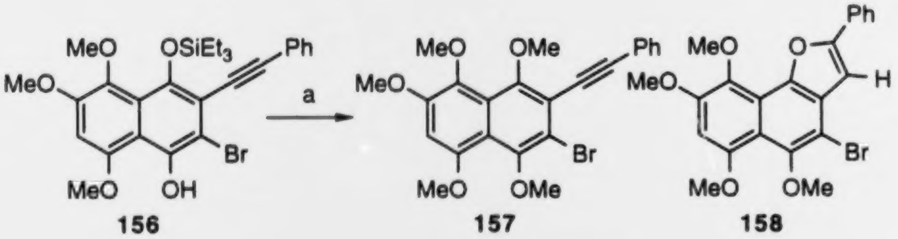
Following our well established procedure,[46] trimethoxynaphthol **120** was converted into bromide **156**, which serves as a useful intermediate for the construction of a diversity of top pieces having various protective groups in ring E (Scheme 35). Fortunately, elaboration of the top piece with both benzyl protective groups on ring F from intermediate **156** required only slight adjustments to the existing methods of synthesis of the EF ring system.

At this stage, we decided to solve a problem that arose in the original protection sequence. When naphthol **156** was converted into pentamethoxy bromide **157** without isolation of the intermediates (Scheme 36), furan **158**, formed by the addition of the hydroxyl anion onto the acetylene in a 5-*endo* manner, was occasionally observed,[46] and



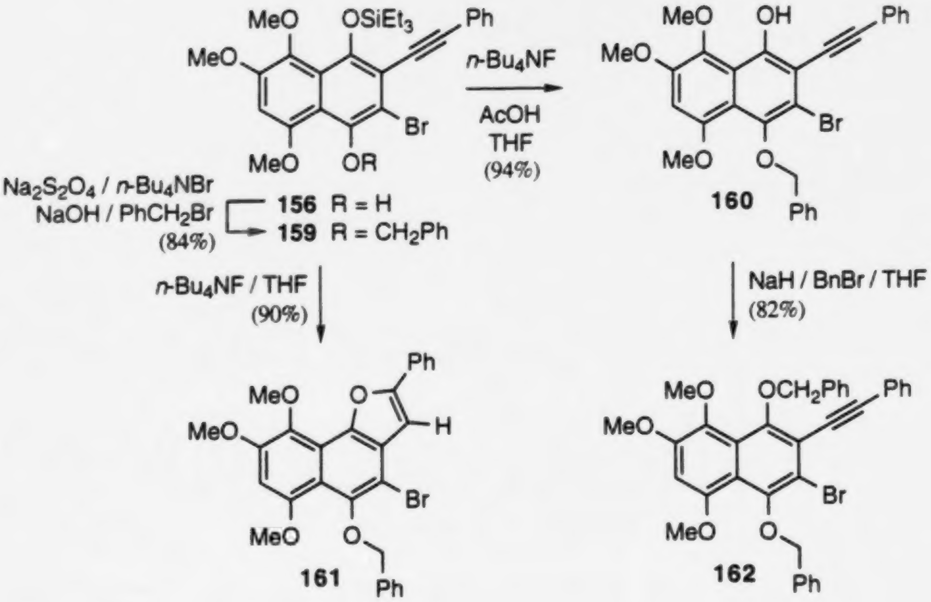
Scheme 35 *Reagents and conditions:* (a) Br_2·dioxane, $CHCl_3$, 0 °C, 97%; (b) $Na_2Cr_2O_7$, H_2SO_4, H_2O, acetone, 0 °C, addition *ca.* 4 h, 55%; (c) phenylacetylene, CuI, $(PPh_3)_4Pd$, *i*-Pr_2NEt, DMF, rt, dark, 18 h, 77%; (d) $Na_2S_2O_4$, *n*-Bu_4NBr, H_2O, CH_2Cl_2; (e) Et_3SiCl, DMAP, Et_3N, CH_2Cl_2, addition 0 °C, rt, overnight, 73% (over two steps); (f) Py·HBr·Br_2,THF, addition -78 °C, rt, 5 h, 66% (reference 46)

the two components of the mixture could not be separated (by chromatography or crystallization). This ring closure was earlier reported as a method for the formation of benzofurans.[54]



Scheme 36 *Reagents and conditions:* (a) $Na_2S_2O_4$, *n*-Bu_4NBr, H_2O, CH_2Cl_2, rt, 10 min, 2 N NaOH, $(MeO)_2SO_2$, rt, overnight; then *n*-Bu_4NF, rt, *ca.* 3 h; then $(MeO)_2SO_2$, rt, overnight, 95% **157** (reference 46)

A controlled synthesis with isolation of all intermediates would be preferable to the one-step procedure. Protection of naphthol **156** gave bromide **159** (Scheme 37). The silicon protective group was cleanly removed (**159**→**160**) by treatment with

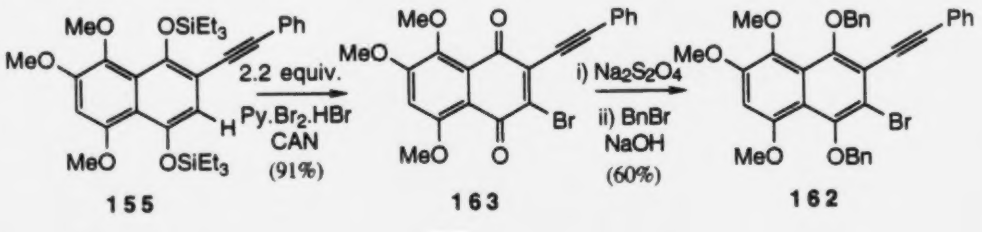


Scheme 37

tetrabutylammonium fluoride in the presence of excess acetic acid.[55] The formation of furan **161** was therefore avoided by *in situ* protonation of the hydroxyl anion. Naphthol **160** was protected by treatment with benzyl bromide and sodium hydride, to give bromide **162**, with no trace (^{1}H NMR) of the furan **161**.

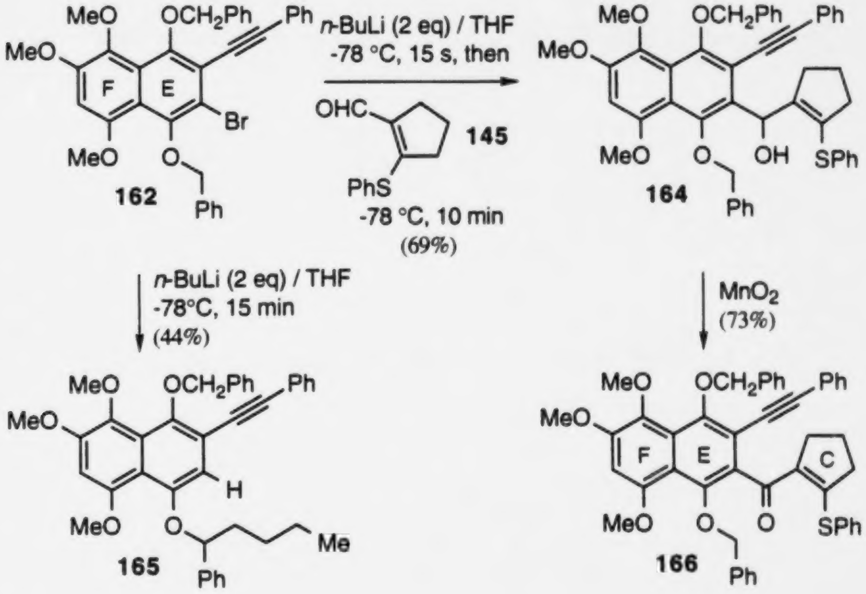
We also repeated the deprotection step omitting the acetic acid, and these conditions led exclusively to the furan (**159→161**).

These experiments show the dramatic effect of the counter-ion. On one hand, the loosely bonded ammonium ion gave rapid cyclization onto the acetylene and on the other hand, the tightly bonded sodium ion species could be trapped intermolecularly.



Scheme 38

Bromide **162** was also obtained by an alternative route (Scheme 38). Treatment of bromide **155** with excess of brominating agent followed by the addition of an oxidizing agent (CAN) gave directly quinone **163**. Reduction of the quinone with sodium hydrosulfite, followed by protection of the intermediate hydroxyquinone, gave bromide **162**.



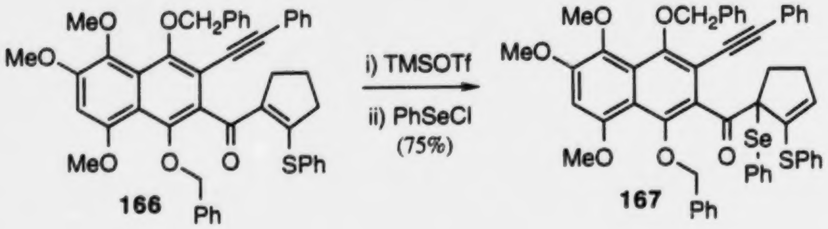
Scheme 39

The coupling of rings EF (**162**) with aldehyde **145**[52,56] proved to be more difficult than anticipated (Scheme 39). Only a small amount of the desired alcohol **164** (*ca.* 30%) was isolated when our standard coupling method was used.[46]

This problem was solved by analysis of the following observation. When a solution of substrate **162** was treated with two equivalents of *n*-butyllithium at -78 °C, and then stirred for 15 minutes, the major product isolated after work up was compound **165**. This reaction of benzyl ethers was known[57] and could potentially limit the use of this protective group under strongly basic conditions.

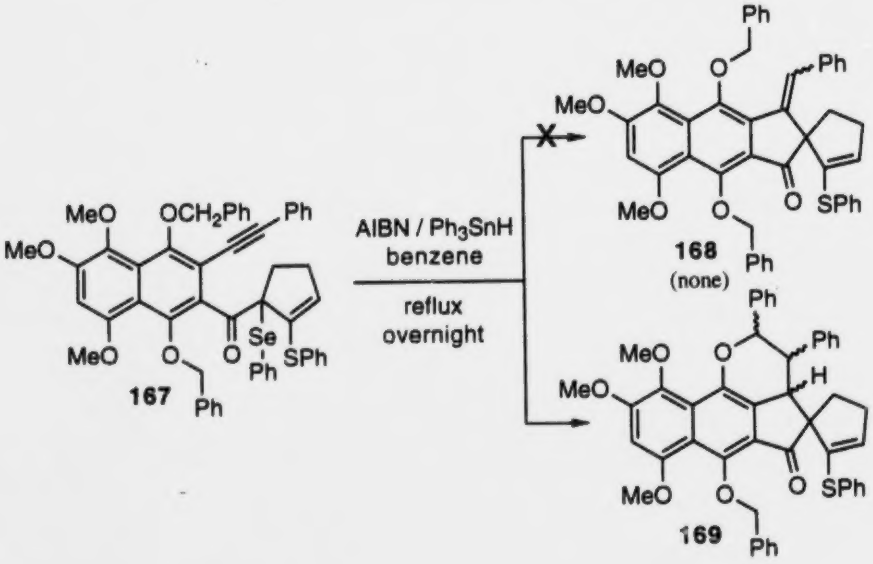
In order to suppress this side reaction, a shorter reaction time was used in the transmetalation. Addition of the same amount of organolithium to a solution of bromide **162** at -78 °C, followed by addition of two equivalents of aldehyde **145** after a *short* (*ca.* 15 s) period, gave the coupled compound **164** in good yield. This alcohol, now available in sufficient quantities, was oxidized with manganese(IV) oxide (**164**→**166**).

Following our plan, ketone **166** was converted into selenide **167**, without isolation of the intermediate silyl enol ether (Scheme 40).



Scheme 40

Under our standard radical spirocyclization conditions, selenide **167** failed to furnish any of the desired spiro compound **168** (Scheme 41). The substrate appeared to

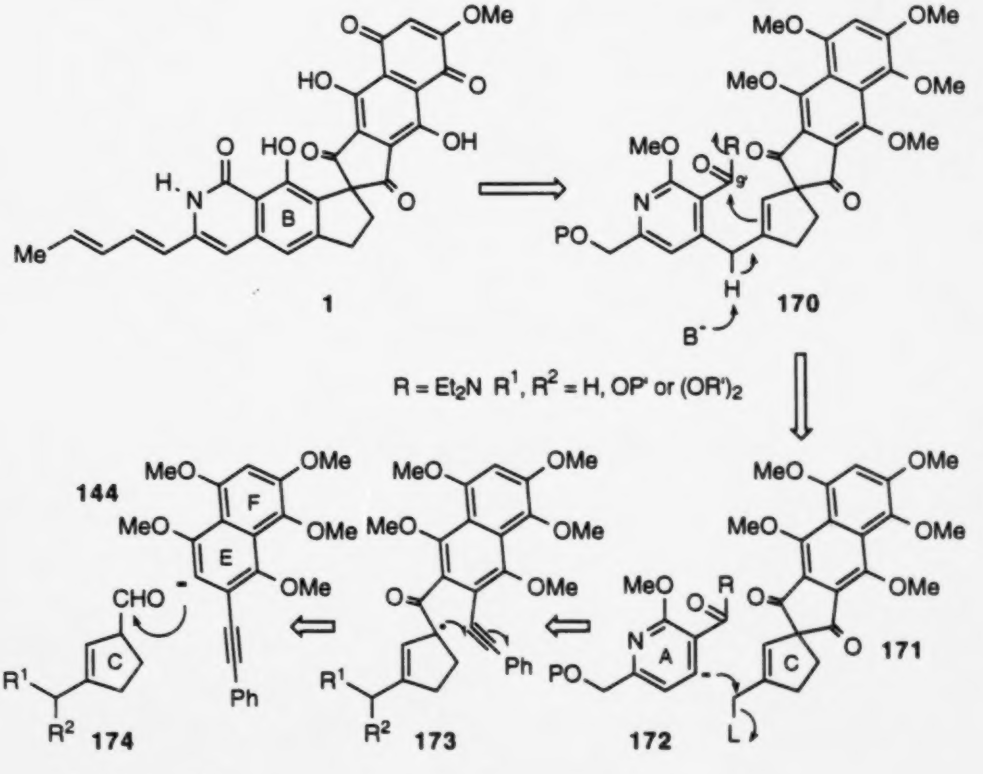


Scheme 41

behave in a similar manner to the previous example in which a benzyl ether was used for protection of a phenolic group, giving a complex mixture [^{1}H NMR] of isomers of the rearranged compound **169**. This substance results from abstraction of the benzylic hydrogen (see mechanism Scheme 23, R = Ph). As previously stated, the rearranged compound **169** cannot be converted into any useful intermediate for the synthesis of fredericamycin A.

Another disappointing result convinced us to abandon this linear approach for the synthesis of fredericamycin A: the coupling reaction (**141** + **142**→**1**, Scheme 33) failed under a variety of reaction conditions.[53]

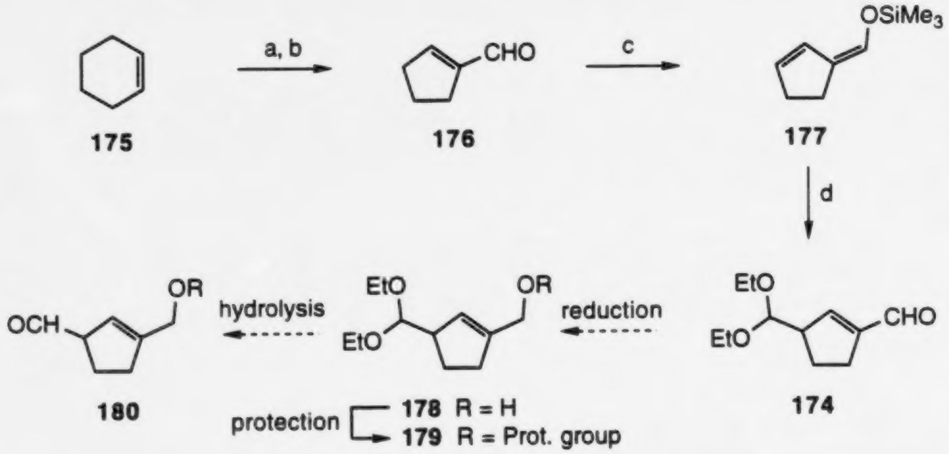
A second linear approach was then considered in which the carbon linking rings A and C would be attached initially to ring C (Scheme 42), contrary to our previous linear



R = Et$_2$N R^1, R^2 = H, OP' or (OR')$_2$

Scheme 42

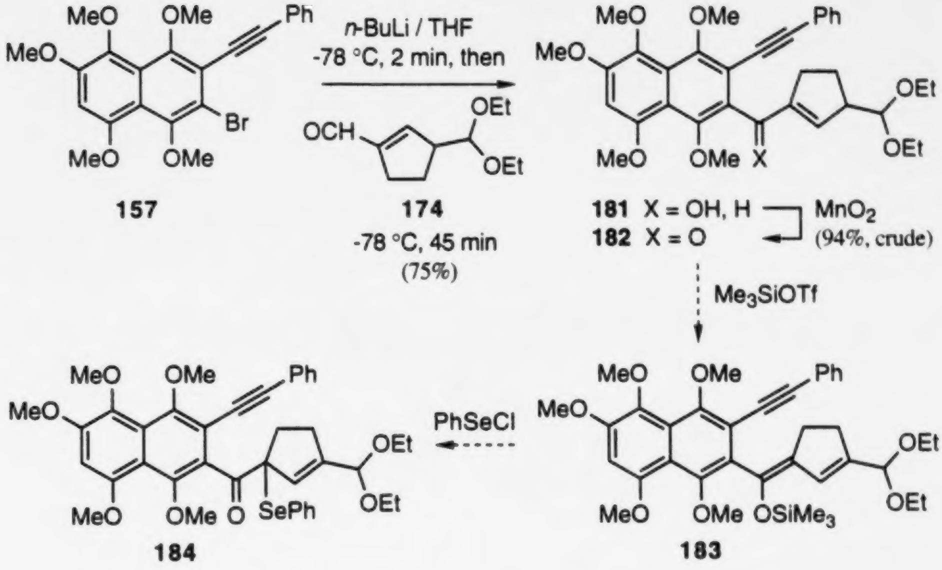
approach in which the carbon having that same function was attached to ring A (Scheme 33). Ring B of fredericamycin A would be formed by addition of an allylic anion to the carbonyl group (C-9') of compound **170**. The coupling would be accomplished by nucleophilic substitution of an allylic leaving group on ring C by the anion of ring A (**172**) (generated by directed *ortho*-lithiation). The northern moiety (**171**) would be accessible by our previous strategy (coupling and radical spirocyclization).



Scheme 43 *Reagents and conditions:* (a) HCOOH, H_2O_2, 55-60 °C, addition 1.5 h, steam dist., 82% (*trans*-cyclohexane-1,2-diol); (b) $NaIO_4$, HNO_3, aq. NaOH (pH 4), H_2O, Et_2O, 20% KOH, rt, 30 min, 58% (reference 59); (c) Et_3N, Me_3SiCl, $ZnCl_2$, benzene, rt, 6 h, 50-60 °C, 2 h, 60%; (d) $ZnCl_2$, $(EtO)_3CH$, rt, 4 h, 48% (reference 58)

Fortunately, a method for the preparation of the required aldehyde **174**[58] ($R^1 = R^2 = Et$) in the first coupling was known (Scheme 43). Aldehyde **174** could be used either directly in the coupling reaction with the top piece, or could be converted, in principle, into aldehyde **180**, which possesses the desired oxidation level in intermediate **171** (Scheme 42).

Having both components for the coupling, the anion derived from bromide **157** was added to aldehyde **174** and the resulting mixture of alcohols **181** was converted into ketone **182** (Scheme 44). When we had reached the stage of compound **182**, the problem of the key coupling (Introduction, Scheme 25, **117** + **118**→**116**) in the main



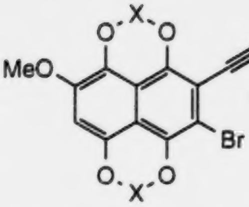
Scheme 44

series leading (eventually) to the total synthesis of fredericamycin A was solved. Since a convergent approach is generally considered more elegant and efficient, the present linear approach was now abandoned.

The Abstraction Problem: The Deuterium Protective Group

In our approach to the total synthesis of fredericamycin A, ring D would be constructed by a radical spirocyclization (Introduction, Scheme 25). We anticipated a problem due to hydrogen abstraction in this series, as it was observed earlier in model studies (Scheme 34, **146**→**148**). Consequently, we needed a means of avoiding formation of the undesired rearranged product.

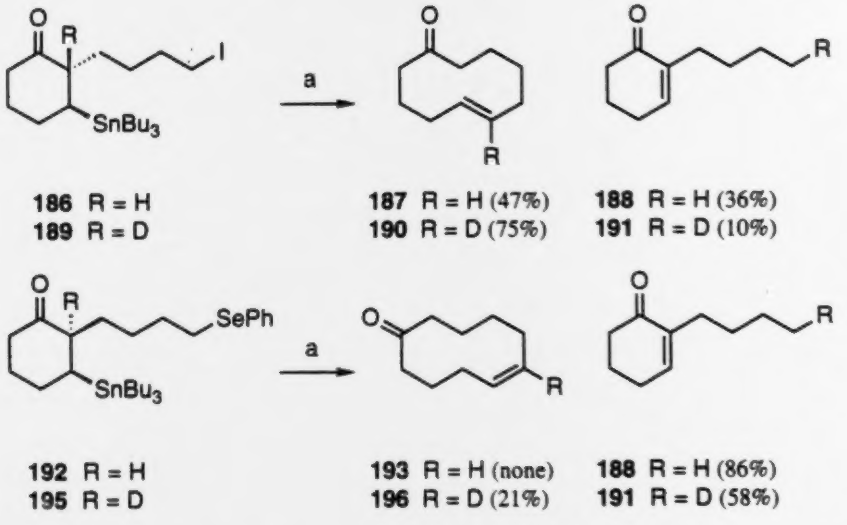
A possible solution to this problem is to limit the accessibility of the vinyl radical to the hydrogen atoms of the protecting groups in ring E. A modification of the protective groups, such as linking the *peri* oxygens (Structure **185**), was considered, but, unfortunately, all attempts by other group members to make such compounds failed.



185 X = SiR_2, CR_2

A second approach to limit the radical abstraction would take advantage of primary isotope effects. The carbon-deuterium bond is stronger[60] than the carbon-hydrogen bond, the energy barrier to homolytic cleavage of the C–D bond being higher. Consequently, a lowering of the abstraction rate constant is expected, and the yield of the rearranged compound should be lower in a series where the abstracted hydrogens are replaced by deuteriums.

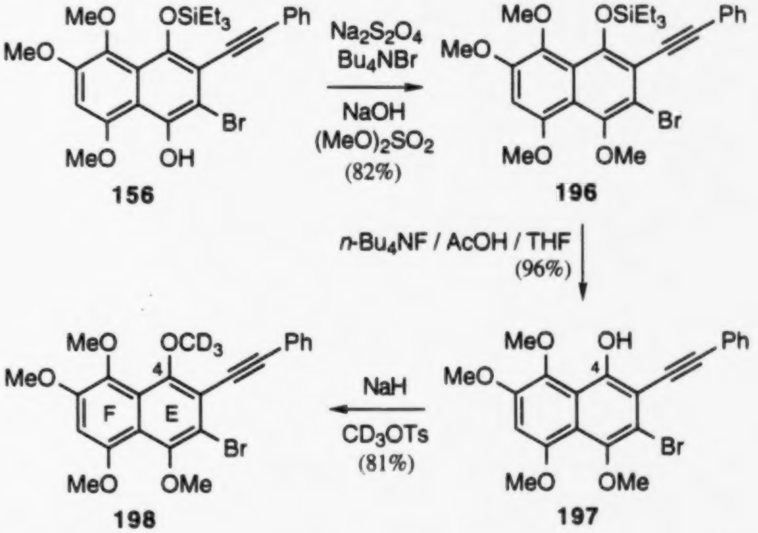
For example, Baldwin[61] has reported the use of isotopic substitution to limit an undesired radical abstraction (Scheme 45). When iodide **186** (R = H) was treated with catalytic amounts of both tributyltin hydride and AIBN, the desired ring expanded product **187** (R = H) was isolated in only 47% yield. By simple substitution of the abstracted hydrogen by deuterium (compound **189**), the yield of the desired compound **190** (R = D)



Scheme 45 *Reagents and conditions:* (a) 0.1 equiv of *n*-Bu_3SnH, 0.2 equiv AIBN, benzene, 80 °C, 2–24 h (reference 61)

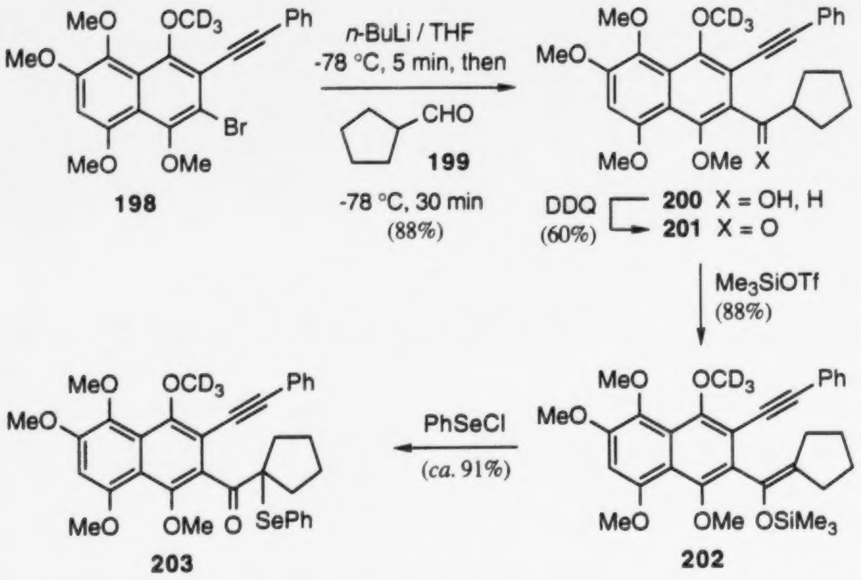
was considerably increased (75%). Similarly, selenide **192** (R = H) gave only the compound of 1,5-hydrogen abstraction **188** (R = H), while compound **195** (R = D) gave a small amount of the medium ring **191** (R = D).

While we were (inexcusably) unaware of this work, we decided to test the concept of discrimination by isotope effects for a desired pathway over a side reaction (Scheme 46). The hydrogen atoms of the methyl ether (where abstraction had previously occurred) were simply substituted by deuterium atoms as the hydroxyl group at position C-4 was protected as a trideuteromethyl ether (Scheme 34). Naphthol **198** was derived from intermediate **156** by a method similar to the one described for the preparation of the *bis* benzyl series (Scheme 37). The free hydroxyl group (C-4) of naphthol **197** was protected by treatment with methyl-d_3 *p*-toluenesulfonate[62] and sodium hydride.[63]



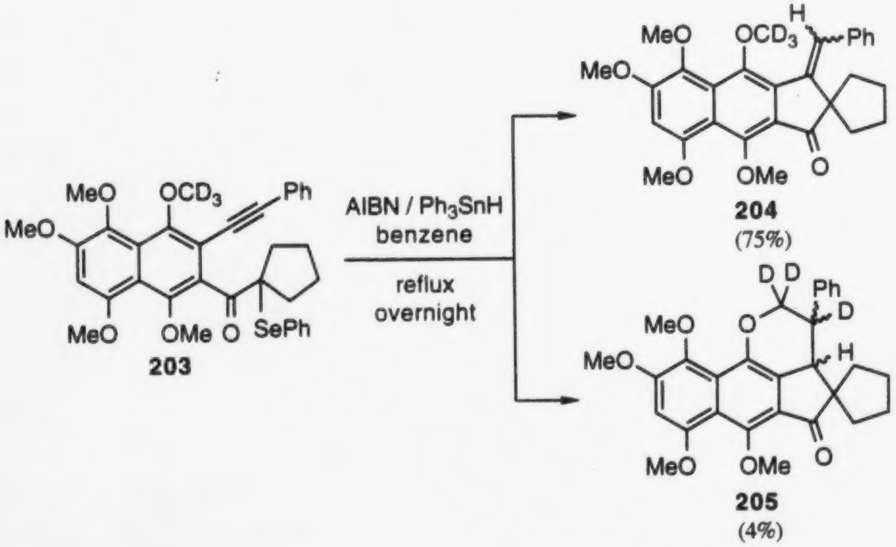
Scheme 46

Conversion of deuterated bromide **198** into the key selenide **203** was accomplished by the route described for the non-deuterated analog,[46] and proceeded with similar yields (Scheme 47).



Scheme 47

When deuterated selenide **203** was treated under our standard radical cyclization conditions (Scheme 48), the desired spiro compound **204** was produced in more than 70% yield, which is a clear improvement over the non-deuterated series (**146→147**,

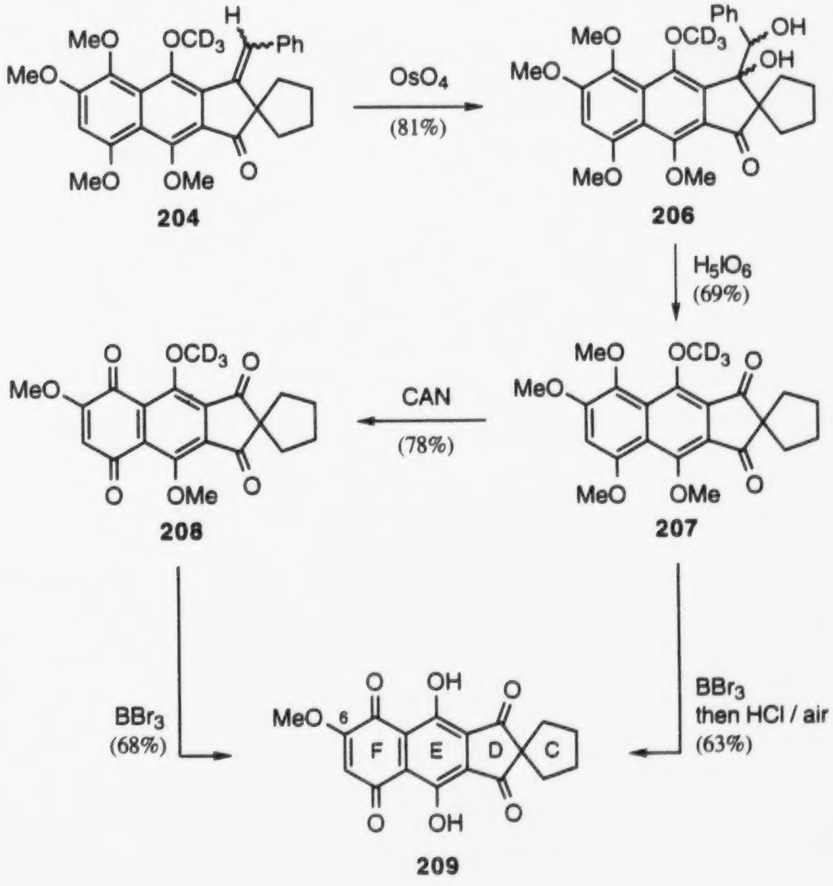


Scheme 48

Scheme 34). Only minute amounts of the rearranged compound **205** were isolated, showing the efficiency of isotope effect in reducing the rate of hydrogen abstraction by the vinyl radical. To our knowledge, this work was the first reported example of the use of isotopic substitution to improve the effectiveness of a protective group.[64]

Degradation of the Spiro Compound

The present model was converted to the C–F rings of fredericamycin A, using a methodology that had been developed in the group for the non-deuterated series (Scheme 49). The exocyclic double bond of ketone **204** was cleaved following our reported

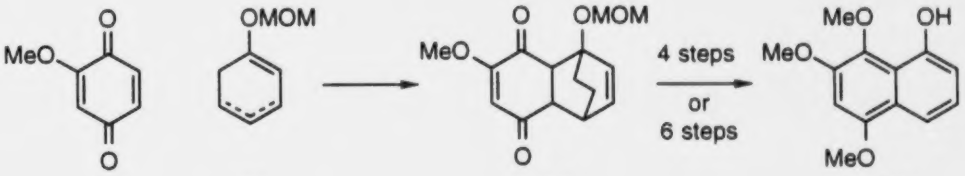


Scheme 49

method[46] to produce diketone **207**. Two routes were then used to complete the degradation. The spiro diketone **207** was treated with ammonium cerium(IV) nitrate[65] (CAN) to give quinone **208** exclusively. Boron tribromide selectively unmasked the methyl ethers in ring E to give spiro diketone **209**, which was identical to the compound obtained in the non-deuterated series. Alternatively, spiro diketone **207** was converted into compound **209** by a more direct route, using boron tribromide for deprotection of only four of the five methoxy groups (leaving position C-6 intact), and exposure to air for the oxidation of ring F.

Conclusions

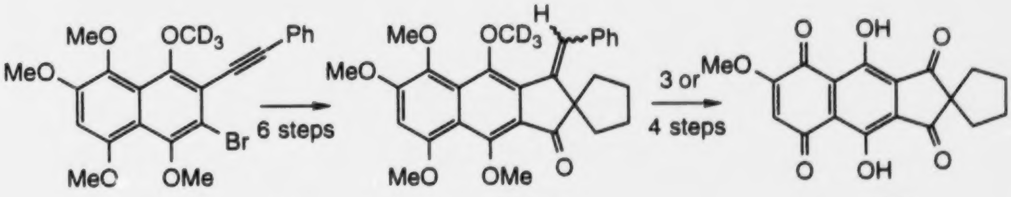
We have been able to prepare an early precursor of the EF rings of fredericamycin A by a simple Diels-Alder approach. The cycloaddition adduct **130** was converted by two routes to the desired naphthol **120** (Scheme 50). Although this method appeared useful at first, a much shorter synthesis is currently in use by our group (see Scheme 32).



123 **128** **130** **120**

Scheme 50

We were also able to alter the course of a radical cyclization reaction by isotopic improvement of a protective group (Scheme 51). By comparison to the original series (Discussion, Scheme 34), the desired spiroketone (**204**) was isolated in higher yield in the modified protective group series. These original results are the main contribution to two publications.[64]



198 **204** **209**

Scheme 51

In our group's total synthesis of fredericamycin A **1**,[66] using the strategy mentioned in the Introduction (Scheme 25), the intramolecular hydrogen abstraction was not observed to a large extent (< 10%) and so isotopic substitution in the protective group was not necessary.

III EXPERIMENTAL

General Procedures. Unless stated to the contrary, the following conditions apply. Reactions were carried out under a slight static pressure of argon that had been purified by passage through a column (3.5 × 42 cm) of R-311 catalyst[67] and then through a similar column of Drierite. Glassware was dried in an oven for at least 2 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and ethyl acetate (EtOAc) used for chromatography were distilled before use. Petroleum ether (refers to the fraction boiling at 60–90 °C), anhydrous ether, dichloromethane, acetone (reagent grade), and glacial acetic acid were used directly without purification.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Melting points were determined on a Kofler block melting point apparatus.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[68] followed by charring on a hot plate, or by examination under UV light. Unless indicated otherwise, silica gel for flash chromatography was Merck type 60 (230–400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry tetrahydrofuran, diethyl ether, benzene and xylenes were distilled from sodium and benzophenone ketyl. Dry triethylamine, dichloromethane, chloroform, acetonitrile, and pyridine were distilled from CaH_2. Commercial (Aldrich) solution of *n*-BuLi was assumed to have the stated molarity.

FT-IR measurements were made as casts from the specified solvent using potassium bromide plates.

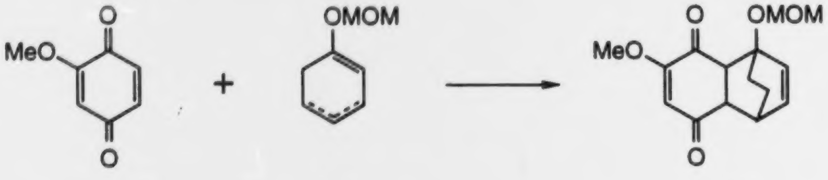
Proton spectra were recorded on Bruker WH-200 (at 200 MHz), Bruker WH-300 (at 300 MHz), or Bruker WH-400 (at 400 MHz) instruments in the specified deuterated solvent. The following abbreviations were used in the text: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

^{13}C NMR spectra were recorded on Bruker WH-300 (at 75.469 MHz) instrument in the specified deuterated solvent. The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

Mass spectra were recorded with an AEI MS–50 mass spectrometer at an ionizing voltage of 70eV.

Microanalyses were performed by the microanalytical laboratory of this Department.

1,4,4a,8a-Tetrahydro-7-methoxy-1-(methoxymethoxy)-1,4-ethanonaphthalene-5,8-dione (130).

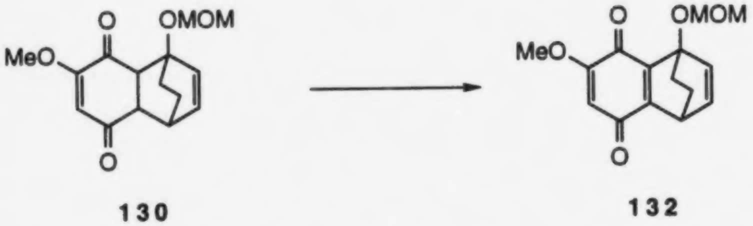


123 **128** **130**

A stirred solution of [1-(methoxymethyl)oxy]cyclohexa-1,3-diene[49] **128** (9.75 g, 75% of the mixture, 52 mmol) and 2-methoxy-1,4-benzoquinone[48] **123** (6.00 g, 34 mmol) in dry PhH (43 mL) was heated at 80 °C for 5 h. The heating bath was removed and the mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (5 × 18 cm), using 1:1 EtOAc–petroleum ether, gave cycloaddition adduct (8.7 g, 73%) as a dark red solid, which was recrystallized from CH_2Cl_2–hexane to give adduct **130** (4.37 g, 36%) as a homogeneous [^{1}H NMR (300 MHz)], beige solid: mp 96–97 °C; FTIR ($CHCl_3$ cast) 2940, 1696, 1654, 1609, 1369, 1233 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300

MHz) δ 1.46–1.70 (m, 2 H), 1.78 (tdd, *J* = 11.5, 4.0, 2.0 Hz, 1 H), 1.96 (td, *J* = 11.5, 3.5 Hz, 1 H), 3.07 (dd, *J* = 7.5, 3.0 Hz, 1 H), 3.13–3.19 (m, 1 H), 3.28 (d, *J* = 8.5 Hz, 1 H), 3.41 (s, 3 H), 3.73 (s, 3 H), 4.72 (d, *J* = 8.0 Hz, 1 H), 5.04 (d, *J* = 8.0 Hz, 1 H), 5.92 (s, 1 H), 6.18 (dd, *J* = 9.0, 7.5 Hz, 1 H), 6.30 (d, *J* = 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 23.97 (t'), 32.20 (t'), 36.04 (d'), 50.88 (d'), 52.35 (d'), 55.54 (q'), 56.17 (q'), 80.29 (s'), 92.12 (t'), 114.31 (d'), 131.69 (d'), 134.27 (d'), 163.85 (s'), 191.12 (s'), 197.67 (s'); exact mass *m/z* calcd for $C_{15}H_{18}O_5$ 278.1154, found 278.1151.

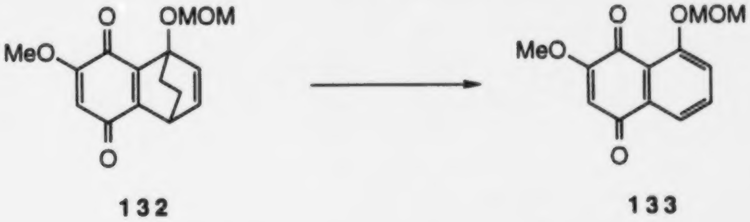
1,4-Dihydro-7-methoxy-1-(methoxymethoxy)-1,4-ethanonaphthalene-5,8-quinone (132).



t-BuOK (636 mg, 95%, 5.38 mmol) was added to a stirred solution of diketone **130** (502 mg, 1.80 mmol) in dry THF (18 mL). Stirring was continued for 2 h, and water (40 mL) was added. The mixture was acidified with 2.0 N aqueous HCl (pH ≈ 3), and then extracted with Et_2O (2 × 40 mL). The combined organic extracts were dried ($MgSO_4$), the solution was transferred into a round-bottomed flask, and silver oxide (1.5 g) was tipped into the solution. The mixture was stirred for 3 h, filtered through a pad of Celite (5 × 2 cm), and evaporated. Flash chromatography of the residue over silica gel (1.8 × 13 cm), using 1:2 EtOAc–hexane, gave quinone **132** (405 mg, 81%) as a slightly impure [^{1}H NMR (300 MHz)], yellow solid: mp 119–121 °C; FTIR ($CHCl_3$ cast) 2946, 1675, 1642, 1610, 1578, 1224 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31–1.43 (m, 1 H), 1.50–1.61 (m, 1 H), 1.64–1.82 (m, 2 H), 3.48 (s, 3 H), 3.76 (s, 3 H), 4.24 (m, 1 H), 4.89 (d, *J* = 8.0 Hz, 1 H), 5.00 (d, *J* = 7.5 Hz, 1 H), 5.73 (s, 1 H), 6.27 (dd, *J* = 8.0, 6.5 Hz, 1

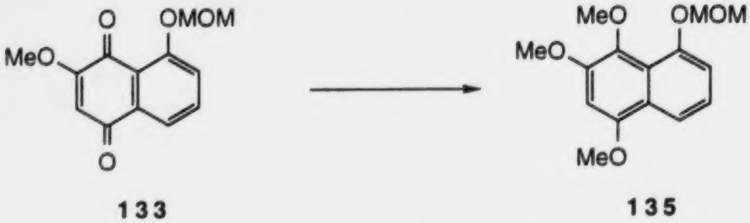
H), 6.79 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 24.71 (t'), 31.63 (t'), 33.49 (q'), 55.46 (q'), 56.46 (q'), 64.50 (s'), 96.37 (t'), 105.10 (d'), 131.19 (d'), 137.20 (d'), 143.01 (s'), 149.20 (s'), 158.71 (s'), 177.49 (s'), 183.34 (s'); exact mass *m/z* calcd for $C_{15}H_{16}O_5$ 276.0998, found 276.0993. Anal. Calcd for $C_{15}H_{16}O_5$ C, 65.21; H, 5.84. Found: C, 65.06; H, 5.62.

2-Methoxy-8-(methoxymethoxy)-1,4-naphthoquinone (133).



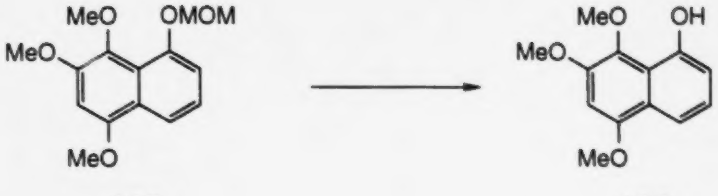
A stirred solution of quinone **132** (121.1 mg, 4.38 mmol) in dry xylenes (5 mL) was heated at 140 °C for 1 h. The solution was cooled to room temperature, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:2 EtOAc–hexane, gave quinone **133** (94.7 mg, 87%) as a pure homogeneous [^{1}H NMR (300 MHz)], yellow solid: mp 151–155 °C (sublimes); FTIR ($CDCl_3$ cast) 1674, 1646, 1611, 1586, 1211 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.53 (s, 3 H), 3.87 (s, 3 H), 5.35 (s, 2 H), 6.10 (s, 1 H), 7.46 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.65 (dd, *J* = 8.5, 7.5 Hz, 1 H), 7.81 (dd, *J* = 7.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 56.47 (q'), 56.71 (q'), 95.19 (t'), 108.12 (d'), 120.27 (d'), 121.79 (d'), 134.34 (s'), 135.16 (d'), 157.58 (s'), 161.04 (s'), 178.50 (s'), 184.63 (s'); exact mass *m/z* calcd for $C_{13}H_{12}O_5$ 248.0684, found 248.0682.

1,2,4-Trimethoxy-8-(methoxymethoxy)naphthalene (135).



A solution of $Na_2S_2O_4$ (0.21 g, 1.21 mmol) and *n*-Bu_4NBr (*ca.* 10 mg) in water (5 mL) was added to a stirred solution of quinone **133** (78 mg, 0.31 mmol) in CH_2Cl_2 (10 mL). Vigorous stirring was continued for 30 min. $(MeO)_2SO_2$ (0.30 mL, 3.2 mmol), followed by 2.0 N aqueous NaOH (1.0 mL, 2.0 mmol) were added, each in one portion, and stirring was continued at room temperature overnight. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using 1:2 Et_2O–hexane, gave substituted naphthalene **135** (53 mg, 61%) as a viscous liquid: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.61 (s, 3 H), 3.85 (s, 3 H), 3.98 (s, 3 H), 4.00 (s, 3 H), 5.28 (s, 2 H), 6.78 (s, 1 H), 7.13 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.23 (dd, *J* = 8.0, 7.5 Hz, 1 H), 7.89 (dd, *J* = 8.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 55.90 (q'), 56.47 (q'), 57.61 (q'), 61.84 (q'), 96.03 (d'), 96.96 (t'), 114.65 (d'), 116.83 (d'), 122.44 (s'), 123.37 (d'), 123.82 (s'), 137.47 (s'), 149.86 (s'), 152.45 (s'), 152.54 (s').

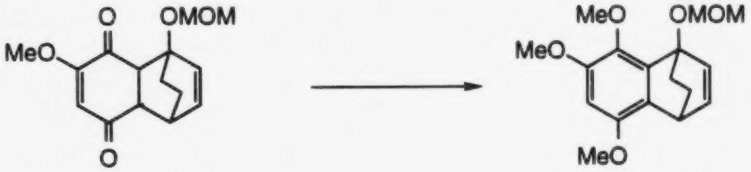
5,7,8-Trimethoxy-1-naphthol (120).



135 **120**

p-TsOH·H_2O (37 mg, 0.19 mmol) was added to a stirred solution of substituted naphthalene **135** (540 mg, 1.9 mmol) in dry MeOH (19 mL). Stirring was continued for 24 h, and the mixture was evaporated. Flash chromatography of the residue over silica gel (1.8 × 14 cm), using 1:2 Et_2O–hexane, gave a greenish solid which was recrystallised from $CHCl_3$–hexane to give the 5,7,8-trimethoxy-1-naphthol **120** (418 mg, 92%) as a pure [^{1}H NMR (300 MHz)], solid which had spectroscopic data identical to the compound prepared by the benzyne approach.[46]

1,4-Dihydro-5,7,8-trimethoxy-1-(methoxymethoxy)-1,4-ethanonaphthalene (137).

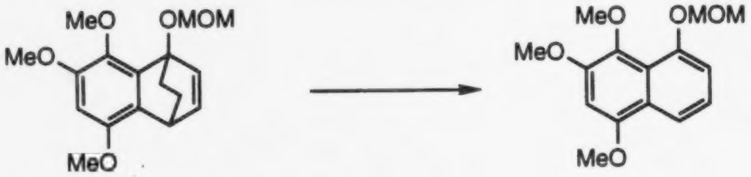


130 **137**

t-BuOK (4.57 g, 97%, 40 mmol) was added to a stirred and cooled (0 °C) solution of recrystallized **130** (4.40 g, 16 mmol) in THF (*ca.* 160 mL). Stirring was continued at 0 °C for 30 min, and $(MeO)_2SO_2$ (10.00 g, 79 mmol) was added dropwise (syringe pump, *ca.* 30 min). The cooling bath was removed, and stirring was continued at room temperature for 2 h. Water (400 mL) was added, and the mixture was extracted with $CHCl_3$ (1 × 400 mL, 2 × 200 mL). The combined organic layers were washed with 1 M aqueous NH_4OH (2 × 200 mL), and water (200 mL). The organic layer was dried

($MgSO_4$) and evaporated. Flash chromatography of the crude residue over silica gel (2.8 × 21 cm), using 3:7 Et_2O–hexane, gave substituted naphthalene **137** (3.89 g, 79%) as a pure [^1H NMR (300 MHz)], yellow solid. A sample was recrystallized twice from Et_2O–pentane for analysis and melting point determination: mp 105–107 °C; FTIR ($CHCl_3$ cast) 2934, 1604, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.49–1.51 and 1.54–1.65 (2 m, 2 H), 1.73–1.82 (m, 2 H), 3.51 (s, 3 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.26 (dtd, J = 6.5, 2.5, 1.5 Hz, 1 H), 4.98–5.13 (m, 2 H), 6.35 (s, 1 H), 6.45 (dd, J = 8.5, 6.5 Hz, 1 H), 6.89 (dd, J = 8.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.81 (t'), 31.99 (d'), 32.52 (t'), 55.07 (q'), 56.29 (q'), 62.92 (q'), 84.47 (s'), 94.99 (d'), 96.30 (t'), 123.76 (s'), 133.80 (d'), 137.53 (s'), 137.60 (d'), 138.06 (s'), 149.09 (s'), 151.54 (s'); exact mass *m/z* calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1471. Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.63; H, 7.24. Found: C, 66.77; H, 7.09.

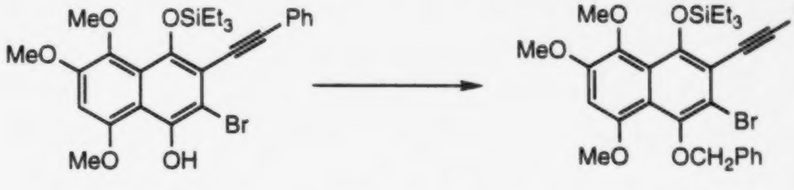
1,2,4-Trimethoxy-8-(methoxymethoxy)naphthalene (138).



137 **138**

A stirred solution of ethanonaphthalene **137** (660 mg, 2.1 mmol) in dry methyl benzoate (4.3 mL), contained in a round-bottomed flask equipped with an air-cooled condenser, was lowered into a preheated oil bath and kept at 200 °C for 3 h. The mixture was cooled, and the solvent was distilled under vacuum (100 °C, 20 mm Hg). Flash chromatography of the residue over silica gel (1.8 × 15 cm), using 1:2 Et_2O–hexane, gave the substituted naphthalene **138** (540 mg, 90%), which had spectroscopic data identical to the compound obtained previously.

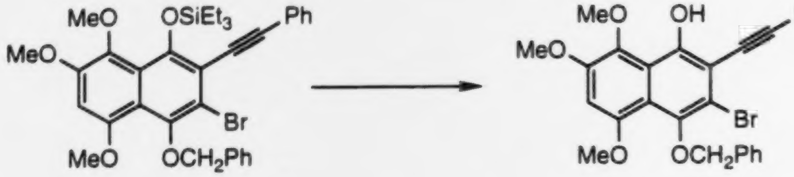
[[3-Bromo-5,7,8-trimethoxy-4-(phenylethynyl)-2-(phenylmethoxy)-1-naphthalenyl]oxy]triethylsilane (159).



156 **159**

A solution of $Na_2S_2O_4$ (0.13 g, 0.75 mmol) and *n*-Bu_4NBr (20 mg, 0.05 mmol) in water (20 mL) was added to a stirred solution of bromide[46] **156** (425 mg, 0.782 mmol) in CH_2Cl_2 (20 mL). Vigorous stirring was continued for 30 min. Benzyl bromide (0.50 mL, 3.9 mmol), followed by 2.0 N aqueous NaOH (1.75 mL, 3.5 mmol) were added, each in one portion, and stirring was continued overnight. CH_2Cl_2 (1 × 60 mL) was added, and the aqueous layer was separated. The organic layer was washed with water (1 × 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 3:17 EtOAc–hexane, gave bromide **159** (414 mg, 84%) as a homogeneous [^{1}H NMR (300 MHz)], yellow solid: mp 99.5–100 °C; FTIR ($CDCl_3$ cast) 2954, 1600, 1548, 1355, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82–1.00 (m, 15 H), 3.74 (s, 3 H), 3.86 (s, 3 H), 4.02 (s, 3 H), 5.00 (s, 2 H), 6.78 (s, 1 H), 7.33–7.48 (m, 6 H), 7.62–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.23 (t'), 6.93 (q'), 56.99 (q'), 57.19 (q'), 61.94 (q'), 75.50 (t'), 87.77 (s'), 97.97 (s'), 99.37 (d'), 115.34 (s'), 117.61 (s'), 123.79 (s'), 124.72 (s'), 127.77 (d'). 128.08 (d'), 128.34 (d'), 128.38 (d'), 131.53 (d'), 137.88 (s'), 138.32 (s'), 146.61 (s'), 149.98 (s'), 150.52 (s'), 152.46 (s'); exact mass *m/z* calcd for $C_{34}H_{37}{}^{81}BrO_5Si$ 634.1574, found 634.1573.

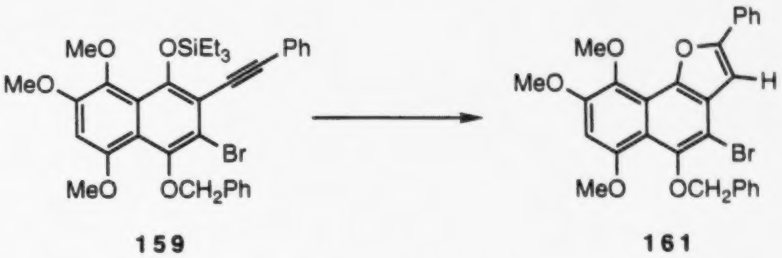
3-Bromo-5,7,8-trimethoxy-2-(phenylethynyl)-4-(phenylmethoxy)-1-naphthalenol (160).



159 **160**

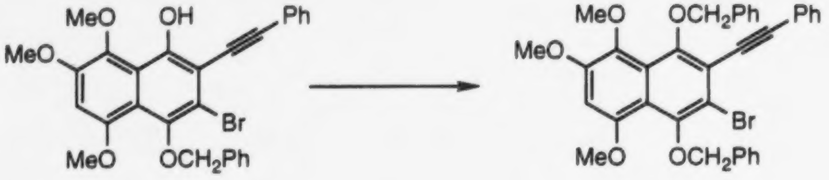
n-Bu_4NF (1.1 mL, 1.0 M in THF, 1.1 mmol) was added rapidly to a stirred solution of bromide **159** (355 mg, 0.56 mmol) in a mixture of dry THF (6 mL) and glacial AcOH (0.32 mL). Stirring was continued at room temperature for 30 min. CH_2Cl_2 (30 mL) was added, and the mixture was washed with water (1 × 10 mL) and saturated aqueous $NaHCO_3$ (1 × 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 20 cm), using 1:2:7 EtOAc–CH_2Cl_2–hexane, gave naphthol **160** (273 mg, 94%) as a homogeneous [^{1}H NMR (200 MHz)] yellow solid: mp 168.5–171 °C; FTIR ($CDCl_3$ cast) 3220, 2925, 1609, 1363, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3 H), 3.98 (s, 3 H), 4.02 (s, 3 H), 4.92 (s, 2 H), 6.69 (s, 1 H), 7.30–7.46 (m, 6 H), 7.60–7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 56.87 (q'), 57.00 (q'), 62.60 (q'), 75.67 (t'), 85.34 (s'), 98.46 (s'), 98.69 (d'), 108.61 (s'), 116.45 (s'), 116.89 (s'), 118.74 (s'), 123.62 (s'), 127.87 (d'), 128.18 (d'), 128.34 (d'), 128.37 (d'), 128.43 (d'), 131.79 (d'), 136.75 (s'), 137.87 (s'), 144.65 (s'), 148.25 (s'), 152.71 (s'), 153.47 (s'); exact mass *m/z* calcd for $C_{28}H_{23}{}^{81}BrO_5$ 520.0709, found 520.0703. Anal. Calcd for $C_{28}H_{23}BrO_5$ C: 64.56; H, 4.57; Br, 15.58. Found: C, 64.75; H, 4.46; Br, 15.38.

4-Bromo-6,8,9-trimethoxy-2-phenyl-5-(phenylmethoxy)naphtho[1,2-*b*]furan (161).



n-Bu$_4$NF (0.17 mL, 1.0 M in THF, 0.17 mmol) was added rapidly to a stirred solution of silyl ether **159** (155 mg, 0.87 mmol) in dry THF (30 mL). Stirring was continued for 90 min. Saturated aqueous NaHCO$_3$ (5 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 × 12 cm), using 1:2:7 EtOAc–CH$_2$Cl$_2$–hexane, gave benzofuran **161** (41 mg, 90%) as a homogeneous [^{1}H NMR (200 MHz)] yellow foam: FTIR (CDCl$_3$ cast) 1589, 1580, 1454, 1346, 1039 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.88 (s, 3 H), 4.03 (s, 3 H), 4.08 (s, 3 H), 5.00, (s, 2 H), 6.72 (s, 1 H), 7.17 (s, 1 H), 7.33–7.52 (m, 6 H), 7.64–7.70 (m, 2 H), 7.93–7.99 (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.469 MHz) δ 57.02 (q'), 57.16 (q'), 61.40 (q'), 76.08 (t'), 97.64 (d'), 102.45 (d'), 105.65 (s'), 114.27 (s'), 119.31 (s'), 124.78 (d'), 127.85 (d'), 128.20 (d'), 128.39 (d'), 128.61 (d'), 128.92 (d'), 130.34 (s'), 135.96 (s'), 137.85 (s'), 144.71 (s'), 148.33 (s'), 150.59 (s'), 153.59 (s'), 156.14 (s'); exact mass *m/z* calcd for $C_{28}H_{23}{}^{79}BrO_5$ 518.0728, found 518.0726.

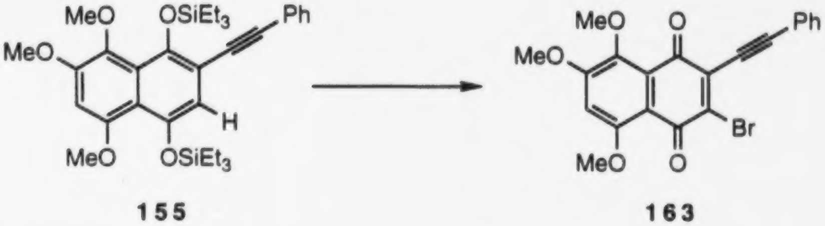
2-Bromo-5,6,8-trimethoxy-3-(phenylethynyl)-1,4-di(phenylmethoxy)naphthalene (162).



160 **162**

A solution of $Na_2S_2O_4$ (73 mg, 0.42 mmol) and *n*-Bu_4NBr (11 mg, 0.04 mmol) in water (10 mL) was added to a stirred solution of naphthol **160** (217 mg, 0.418 mmol) in CH_2Cl_2 (10 mL). Vigorous stirring was continued for 30 min. Benzyl bromide (0.25 mL, 1.2 mmol), followed by 2.0 N aqueous NaOH (0.9 mL, 1.8 mmol) were added, each in one portion, and stirring was continued for 24 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:2:7 EtOAc–CH_2Cl_2–hexane, gave bromide **162** (210 mg, 82%) as a homogeneous yellow solid: mp 126–129 °C; FTIR ($CDCl_3$ cast) 2927, 1599, 1453, 1349, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3 H), 3.86 (s, 3 H), 4.02 (s, 3 H), 5.00 (s, 2 H), 5.18 (s, 2 H), 6.81 (s, 1 H), 7.30–7.48 (m, 11 H), 7.53–7.66 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 56.70 (q'), 57.19 (q'), 62.44 (q'), 75.64 (t'), 77.18 (t'), 85.99 (s'), 98.64 (s'), 98.89 (d'), 115.20 (s'), 117.59 (s'), 119.19 (s'), 123.29 (s'), 125.61 (s'), 127.85 (d'), 127.91 (d'), 128.17 (d'), 128.31 (d'), 128.34 (d'), 128.42 (d'), 128.59 (d'), 128.83 (d'), 131.82 (d'), 137.10 (s'), 137.68 (s'), 137.82 (s'), 149.09 (s'), 150.79 (s'), 153.03 (s'), 153.18 (s'); exact mass *m/z* calcd for $C_{35}H_{29}{}^{79}BrO_5$ 608.1198, found 608.1205. Anal. Calcd for $C_{35}H_{29}BrO_5$: C, 68.97; H, 4.80; Br, 13.11. Found: C, 68.80; H, 4.81; Br, 13.35.

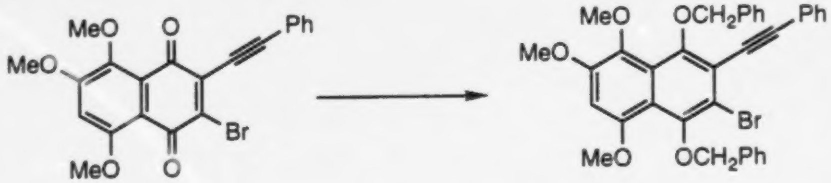
2-Bromo-5,6,8-trimethoxy-3-(phenylethynyl)-1,4-naphthoquinone (163).



Py·HBr·Br_2 (906 mg, 2.83 mmol) was tipped into a stirred and cooled (-78 °C) solution of silyl ether **155** (745 mg, 1.29 mmol) in dry THF (60 mL). Stirring was continued at -78 °C for 45 min. The cooling bath was then removed, and the mixture was stirred for 30 min. CAN (706 mg, 1.29 mmol) was added, and stirring was maintained for an additional 2 h. The mixture was diluted with CH_2Cl_2 (200 mL), and washed with aqueous 10% $^{w}/_{v}$ $Na_2S_2O_3$ (1 × 100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Gravity chromatography of the residue over silica gel* (2.5 × 20 cm), using 1:49 acetone–hexane, gave quinone **163** (499 mg, 91%) as a homogeneous [^{1}H NMR (200 MHz)], red solid: mp 238.5–239.5 °C FTIR ($CHCl_3$ cast) 2200, 1671, 1649, 1573, 1549, 1355, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.93 (s, 3 H), 4.01 (s, 6 H), 6.77 (s, 1 H), 7.35–7.46 (m, 3 H), 7.64–7.72 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 56.36 (q'), 56.87 (q'), 61.57 (q'), 84.49 (s'), 101.49 (d'), 107.30 (s'), 111.94 (s'), 121.99 (s'), 126.23 (s'), 128.51 (d'), 129.98 (d'), 132.41 (d'), 134.91 (s'), 142.58 (s'), 144.25 (s'), 158.75 (s'), 160.27 (s'), 174.86 (s'), 178.65 (s'); exact mass *m/z* calcd for $C_{21}H_{15}{}^{79}BrO_5$ 426.0104, found 426.0098. Anal. Calcd for $C_{21}H_{15}BrO_5$: C, 59.04; H, 3.53. Found: C, 58.73; H, 3.73.

*A course grade of silica gel was used.

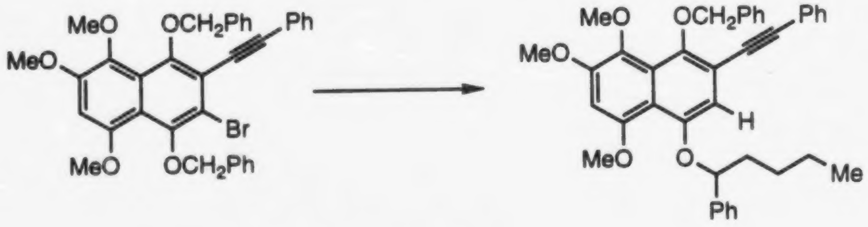
2-Bromo-5,6,8-trimethoxy-3-(phenylethynyl)-1,4-di(phenylmethoxy)naphthalene (163).



163 **162**

A solution of $Na_2S_2O_4$ (1.01 g, 5.8 mmol) and *n*-Bu_4NBr (60 mg, 0.23 mmol) in water (25 mL) was added to a stirred solution of bromoquinone **163** (495 mg, 1.16 mmol) in CH_2Cl_2 (25 mL). Vigorous stirring was continued for 15 min. Benzyl bromide (0.70 mL, 5.85 mmol), followed by 2.0 N aqueous NaOH (3.0 mL, 6.0 mmol) were added, each in one portion, and stirring was continued overnight. CH_2Cl_2 (1 × 100 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 15 cm), using 1:2:7 EtOAc–CH_2Cl_2–hexane, gave bromide **162** (422 mg, 60%) as a homogeneous [^1H NMR (300 MHz)] yellow solid, which had spectroscopic data identical to those for the compound obtained previously.

5,6,8-Trimethoxy-3-(phenylethynyl)-4-(phenylmethoxy)-1-[1-(phenylpentyl)oxy]naphthalene (165).

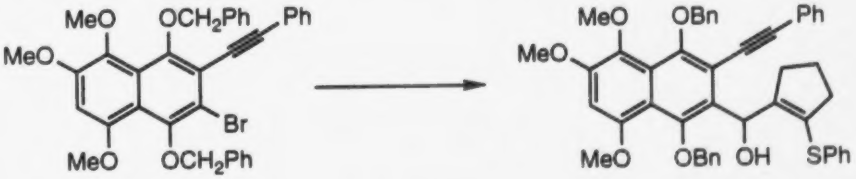


162 **165**

n-BuLi (0.15 mL, 1.6 M in hexanes, 0.24 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **162** (122.0 mg, 0.200 mmol) in dry THF (10 mL).

Stirring was continued at -78 °C for 1 h, and saturated aqueous NH_4Cl (5 mL) was added. The cooling bath was removed, and the mixture was allowed to reach room temperature. Water (25 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using 1:2:7 EtOAc–CH_2Cl_2–hexane, gave rearranged compound **165** (51.2 mg, 44%) as a [^{1}H NMR (300 MHz)] red oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.28–1.53 (m, 4 H), 1.87–2.01 (m, 1 H), 2.03–2.18 (m, 1 H), 3.72 (s, 3 H), 3.97 (s, 3 H), 4.02 (s, 3 H), 5.06 (s ,2 H), 5.26 (t, J = 6.0 Hz, 1 H), 5.60 (s, 1 H), 5.79 (s, 1 H), 7.26–7.39 (m, 9 H), 7.40–7.47 (m, 4 H), 7.63–7.69 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.13 (q'), 22.73 (t'), 27.55 (t'), 38.05 (t'), 56.68 (q'), 57.47 (q'), 62.38 (q'), 81.27 (d'), 87.32 (s'), 93.83 (s'), 98.58 (d'), 109.83 (d'), 115.64 (s'), 115.89 (s'), 123.57 (s'), 126.42 (d'), 127.38 (d'), 127.64 (d'), 128.22 (d'), 128.27 (d'), 128.46 (d'), 128.91 (d'), 131.76 (d'), 136.95 (s'), 138.32 (s'), 142.15 (s'), 149.58 (s'), 150.61 (s'), 151.73 (s'), 154.93 (s'); exact mass m/z calcd for $C_{39}H_{38}O_5$ 586.2712, found 586.2702.

α-(2-Phenylthio-1-cyclopenten-1-yl)-[5,6,8-trimethoxy-3-(phenylethynyl)-1,4-di(phenylmethoxy)-2-naphthalenyl]methanol (164).

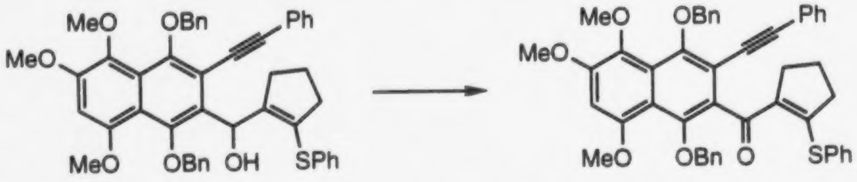


162 **164**

n-BuLi (0.15 mL, 1.6 M in hexanes, 0.24 mmol) was added quickly to a stirred and cooled (-78 °C) solution of bromide **162** (121 mg, 0.20 mmol) in dry THF (5 mL). The mixture was stirred at -78 °C for 15 s, and a solution of aldehyde[52] **145** (70 mg , 0.34 mmol) in THF (1 mL) was injected rapidly. The brown color faded within 30 s. Stirring was continued at -78 °C for 10 min, and the mixture was quenched with saturated aqueous

NH_4Cl (5 mL). The cooling bath was removed, and the mixture was allowed to reach room temperature. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:2:7 EtOAc–CH_2Cl_2–hexane, gave **164** (101 mg, 69%) as a homogeneous [^{1}H NMR (200 MHz)] yellow foam: FTIR ($CDCl_3$ cast) 3542, 2934, 1601, 1582 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62–1.87 (m, 2 H), 2.32–2.41 (m, 2 H), 2.46–2.75 (m, 2 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 4.02 (s, 3 H), 4.27 (m, 1 H), 5.00 (s, 2 H), 5.12 (s, 2 H), 6.47 (d, J = 7.5 Hz, 1 H), 7.09–7.22 (m, 5 H), 7.25–7.46 (m, 1 H), 7.54–7.60 (m, 2 H), 7.61–7.69 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 22.05 (t'), 35.27 (t'), 37.71 (t'), 56.73 (q'), 57.03 (q'), 62.39 (q'), 69.04 (d'), 79.86 (t'), 77.28 (t'), 85.41 (s'), 98.59 (d'), 99.59 (s'), 115.74 (s'), 117.03 (s'), 123.13 (s'), 125.92 (s'), 126.37 (d'), 127.40 (d'), 127.60 (d'), 128.18 (d'), 128.28 (d'), 128.34 (d'), 128.50 (d'), 128.65 (d'), 129.50 (s'), 130.49 (s'), 130.97 (d'), 131.69 (d'), 134.72 (s'), 137.04 (s'), 138.00 (s'), 138.08 (s'), 145.74 (s'), 149.52 (s'), 150.61 (s'), 153.46 (s').

(2-Phenylthio-1-cyclopenten-1-yl)-[5,6,8-trimethoxy-3-(phenylethynyl)-1,4-di(phenylmethoxy)-2-naphthalenyl]methanone (166).

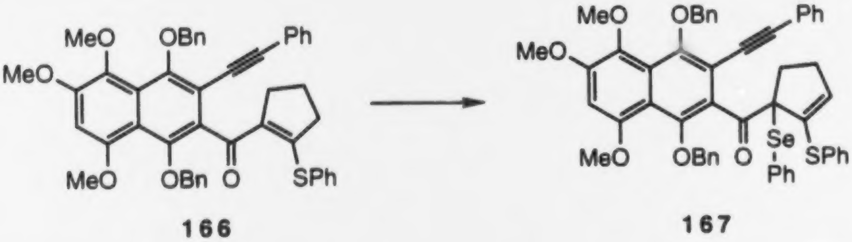


164 **166**

Activated MnO_2 (89 mg, 1.0 mmol) was added to a stirred solution of alcohol **164** (75 mg, 0.10 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 24 h, and filtered through a pad of Celite (1 × 1 cm). The pad was washed with CH_2Cl_2 (30 mL), and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:2:7 EtOAc–CH_2Cl_2–hexane, gave ketone **166** (33 mg, 73%) as

a homogeneous [^{1}H NMR (200 MHz)] yellow foam: FTIR ($CDCl_3$ cast) 2926, 2342, 1633, 1601, 1355, 1339 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73 (pentet, *J* = 7.5 Hz, 2 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 2.70 (t, *J* = 7.5 Hz, 2 H), 3.79 (s, 3 H), 3.90 (s, 3 H), 4.04 (s, 3 H), 5.05 (s, 2 H), 5.19 (s, 2 H), 6.81 (s, 1 H), 7.27–7.53 (m, 16 H), 7.53–7.59 (m, 2 H), 7.73–7.78 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 22.52 (t'), 33.79 (t'), 39.21 (t'), 56.91 (q'), 56.83 (q'), 60.38 (s'), 62.38 (q'), 77.42 (s'), 78.45 (s'), 84.41 (s'), 98.01 (d'), 113.66 (s'), 117.39 (s'), 123.46 (s'), 126.48 (s'), 127.38 (d'), 127.72 (d'), 127.83 (d'), 128.28 (d'), 128.36 (d'), 128.56 (d'), 128.64 (d'), 128.84 (d'), 128.98 (d'), 129.04 (d'), 130.96 (d'), 131.85 (d'), 132.43 (s'), 133.12 (s'), 133.35 (s'), 134.98 (d'), 137.03 (s'), 137.95 (s'), 138.00 (s'), 147.86 (s'), 150.95 (s'), 152.53 (s'), 153.91 (s'), 157.79 (s'), 194.18 (s').

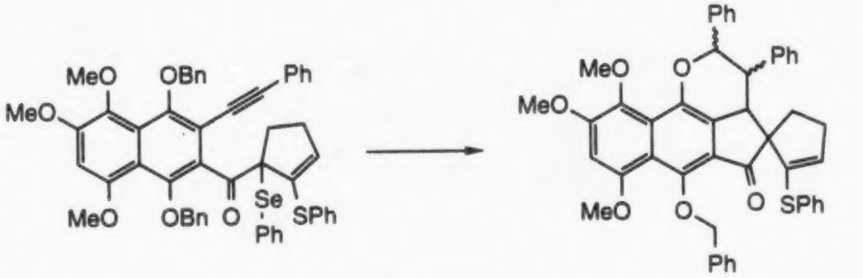
[(1-Phenylseleno-2-phenylthio)-1-cyclopenten-1-yl]-[5,6,8-trimethoxy-3-(phenylethynyl)-1,4-di(phenylmethoxy)-2-naphthalenyl]methanone (167).



Me$_3$SiOTf (15 drops) was added dropwise to a stirred and cooled (0 °C) solution of ketone **167** (51 mg, 0.070 mmol) in dry CH_2Cl_2 (5 mL). Stirring was continued at 0 °C for 10 min, the mixture was cooled to -78 °C, and PhSeCl (40 mg, 0.21 mmol) was tipped into the cooled solution. Stirring was continued at -78 °C for 15 min. The cooling bath was removed, and the mixture was stirred an additional 15 min. EtOAc (10 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 12 cm), using 1:2:7 EtOAc–CH_2Cl_2–hexane, gave selenide **167** (46.5 mg, 75%)

as a homogeneous [^{1}H NMR (200 MHz)] yellow foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.99 (dd, *J* = 13.5, 7.0 Hz, 1 H), 2.11–2.26 (m, 1 H), 2.48 (dd, *J* = 16.0, 8.0 Hz, 1 H), 2.63–2.76 (m, 1 H), 3.78 (s, 3 H), 3.89 (s, 3 H), 3.97–4.06 (m, 1 H), 4.04 (s, 3 H), 5.04 (s, 2 H), 5.15–5.24 (m, 2 H), 6.80 (s, 1 H), 6.98–7.17 (m, 5 H), 7.26–7.47 (m, 13 H), 7.47–7.62 (m, 5 H), 7.69–7.76 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 32.20 (t'), 32.34 (t'), 54.15 (d'), 56.73 (q'), 56.91 (q'), 62.43 (q'), 78.45 (s'), 84.37 (s'), 98.12 (d'), 98.41 (s'), 113.66 (s'), 117.37 (s'), 123.31 (s'), 126.63 (s'), 127.77 (d'), 127.82 (d'), 128.30 (d'), 128.37 (d'), 128.43 (d'), 128.82 (d'), 128.95 (d'), 129.02 (d'), 129.60 (s'), 131.70 (s'), 132.00 (d'), 132.86 (s'), 135.08 (d'), 1335.23 (d'), 135.54 (s'), 137.09 (s'), 137.96 (s'), 148.12 (s'), 151.10 (s'), 152.60 (s'), 153.97 (s'), 155.95 (s'), 191.26 (s'); mass (EI) *m/z* calcd for $C_{53}H_{44}O_6S^{80}Se$ M$^+$ 887, found 887.

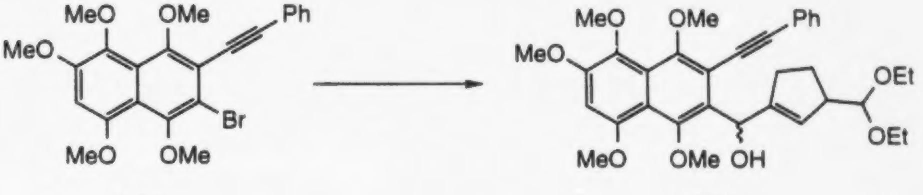
3,3a-Dihydro-7,9,10-trimethoxy-2,3-diphenyl-6-(phenylmethoxy)-spiro[4*H*-benz[5,6]indeno[7,1-*bc*]pyran-4,1'-cyclopent-1-en]-5(2*H*)-one (169).



167 **169**

AIBN (a few crystals) was added to a stirred solution of selenide **167** (46.5 mg, 0.052 mmol) in dry PhH (0.7 mL). The mixture was heated at 80 °C, and a solution of Ph_3SnH (33 mg, 0.094 mmol) in benzene (0.3 mL) was added as soon as the solution started to reflux. The resulting mixture was heated overnight, cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using increasing amounts of EtOAc–CH_2Cl_2 in hexanes [from (1:2:17) to (1:2:7)], gave three major compounds, all in low yield (*ca.* 25%). None of the isolated products had the expected characteristic of the desired compound **168**, and are tentatively assigned as isomers of compound **169**, based on precedents.

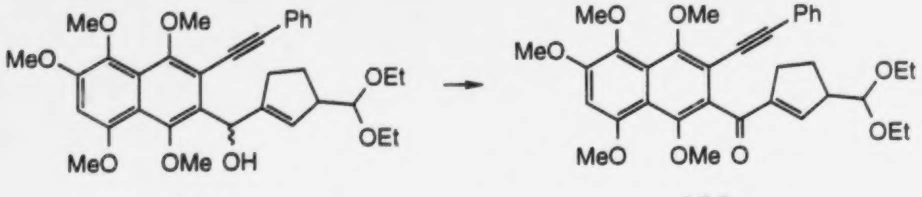
α-[3-Diethoxymethyl-1-cyclopenten-1-yl]-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]methanol (181).



157 **181**

n-BuLi (0.55 mL, 1.6 M in hexanes, 0.88 mmol) was added to a stirred and cooled (-78 °C) solution of bromide **157** (320 mg, 0.70 mmol) in dry THF (6 mL). The mixture was stirred at -78 °C for 2 min, and a solution of aldehyde[58] **174** (278 mg, 1.40 mmol) in dry THF (0.5 mL plus 0.5 mL as a rinse) was injected rapidly. The resulting mixture was stirred at -78 °C for 45 min, and saturated aqueous NH_4Cl (5 mL) was added. The cooling bath was removed, and the mixture was allowed to reach room temperature. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using increasing amounts of EtOAc in hexane (from 10% to 40%), gave alcohol **181** (306 mg, 75%) as a foam. This material was used directly in the next step, without characterization.

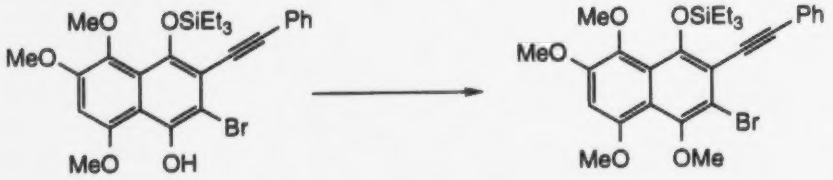
α-[3-Diethoxymethyl-1-cyclopenten-1-yl]-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]methanone (182).



181 **182**

Activated MnO_2 (0.46 g, 5.3 mmol) was added to a stirred solution of alcohol **181** (306 mg, 0.53 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature overnight, and then filtered through a pad of Celite (1 × 1 cm). The pad was washed with CH_2Cl_2 (2 × 25 mL), and the filtrate was evaporated to give crude ketone **182** (288 mg, 94%) as a yellow foam, which was not purified. Ketone **182** had: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, *J* = *ca.* 12 Hz, 3 H), 1.13 (t, *J* = *ca.* 12 Hz, 3 H), 1.72–1.93 (m, 1 H), 1.99–2.22 (m, 1 H), 2.60–2.94 (m, 2 H), 3.05–3.25 (m, 1 H), 3.31–3.68 (m, 4 H), 3.76 (s, 3 H), 3.87 (s, 3 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 4.03 (s, 3 H), 4.20 (d, *J* = *ca.* 12 Hz, 1 H), 6.33–6.37 (m, 1 H), 6.77 (s, 1 H), 7.26–7.37 (m, 3 H), 7.38–7.52 (m, 2 H).

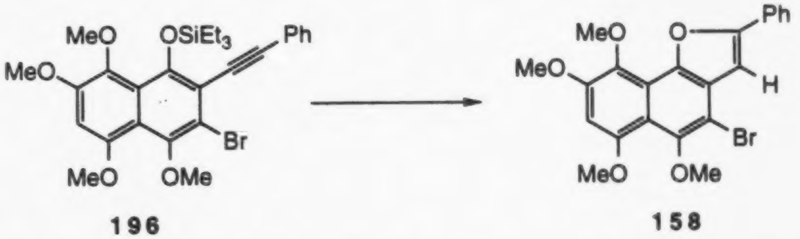
[[3-Bromo-4,5,7,8-tetramethoxy-2-(phenylethynyl)-1-naphthalenyl]oxy]triethylsilane (198).



156 **196**

A solution of $Na_2S_2O_3$ (2.03 g, 12 mmol) and *n*-Bu_4NBr (100 mg, 0.31 mmol) in water (50 mL) was added to a solution of naphthalenol **156** (2.43 g, 4.5 mmol) in CH_2Cl_2 (150 mL). Vigorous stirring was continued for 30 min. $(MeO)_2SO_2$ (4.0 mL, 24 mmol), followed by 2.0 N aqueous NaOH (21 mL, 42 mmol) were added, each in one portion, and stirring was continued overnight. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with 10% aqueous NH_4OH (1 × 50 mL) and with water (1 × 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 × 18 cm), using increasing amounts of EtOAc in hexane (from 10% to 20%), gave **196** (2.05 g, 82%) as a homogeneous [^{1}H NMR (300 MHz)] yellow solid: FTIR ($CHCl_3$ cast) 1600, 1357 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78–0.96 (m, 15 H), 3.70 (s, 3 H), 3.83 (s, 3 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 6.66 (s, 1 H), 7.33–7.43 (m, 3 H), 7.61–7.67 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.25 (t'), 6.92 (q'), 57.27 (q'), 61.52 (q'), 61.93 (q'), 87.76 (s'), 97.91 (s'), 99.63 (d'), 115.26 (s'), 115.47 (s'), 117.48 (s'), 123.82 (s'), 124.70 (s'), 128.36 (d'), 131.53 (d'), 138.43 (s'), 148.16 (s'), 150.00 (s'), 150.13 (s'), 152.44 (s'); exact mass *m/z* calcd for $C_{28}H_{33}{}^{79}BrO_5Si$ 556.1280, found 556.1272. A small portion was recrystallized from CH_2Cl_2–petroleum ether: mp 99–101 °C. Anal. Calcd for $C_{28}H_{33}BrO_5Si$: C, 60.32; H, 5.97. Found: C, 60.30; H, 5.85.

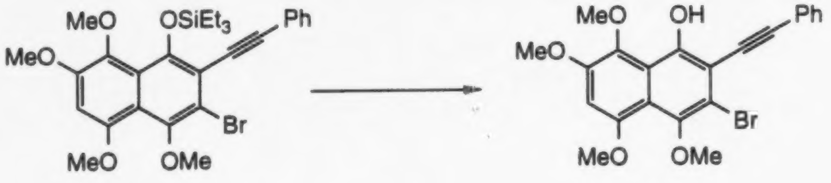
4-Bromo-5,6,8,9-tetramethoxy-2-phenylnaphtho[1,2-*b*]furan (158).



n-Bu_4NF (0.37 mL, 1.0 M in THF, 0.37 mmol) was added to a stirred solution of silane **196** (105 mg, 0.19 mmol) in dry THF (2 mL) at room temperature. Stirring was continued for 2 h. Saturated $NaHCO_3$ (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (1 × 50 mL, 2 × 25 mL). The combined organic extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 18 cm), using 1:4 EtOAc–hexane, gave compound **158** (82 mg, 98%) as a thick oil: FTIR ($CHCl_3$ cast) 2838, 1580, 1456, 1347, 1327, 1220, 1047, 1040, 760 cm^{-1}; ^{1}H NMR

($CDCl_3$, 300 MHz) δ 3.91 (s, 3 H), 4.02 (s, 3 H), 4.05 (s, 3 H), 4.08 (s, 3 H), 6.75 (s, 1 H), 7.17 (s, 1 H), 7.32–7.40 (m, 1 H), 7.44–7.52 (m, 2 H), 7.93–7.99 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 57.01 (q'), 57.34 (q'), 63.36 (q'), 61.88 (q'), 91.68 (d'), 102.36 (d'), 105.15 (s'), 114.07 (s'), 119.24 (s'), 124.74 (d'), 128.14 (s'), 128.58 (d'), 128.88 (d'), 130.31 (s'), 135.95 (s'), 144.54 (s'), 149.80 (s'), 150.57 (s'), 153.42 (s'), 156.09 (s'); exact mass *m/z* calcd for $C_{22}H_{15}{}^{81}BrO_7$ 476.0294, found 476.0277.

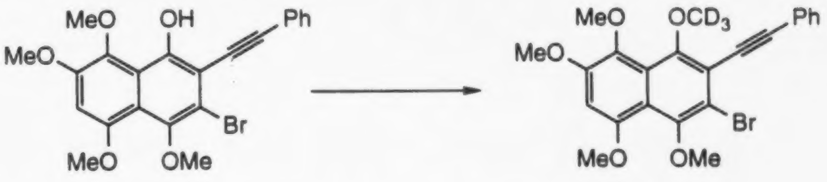
3-Bromo-4,5,7,8-tetramethoxy-2-(phenylethynyl)-1-naphthalenol (199).



196 **197**

n-Bu_4NF (6.9 mL, 1.0 M in THF, 6.9 mmol) was added rapidly to a stirred solution of silyl ether **196** (1.92 g, 3.4 mmol) in a mixture of dry THF (30 mL) and glacial AcOH (2.0 mL). Stirring at room temperature was continued for 30 min. CH_2Cl_2 (150 mL) was added, and the mixture was washed with water (1 × 100 mL), saturated aqueous $NaHCO_3$ (1 × 100 mL), and water (1 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 20 cm), using increasing amounts of EtOAc in hexane (from 20% to 35%), gave naphthol **197** (1.47 g, 96%) as a homogeneous [^1H NMR (200 MHz)] yellow solid: mp 154–155 °C; FTIR ($CHCl_3$ cast) 3230, 1809, 1383, 1343, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 3.82 (s, 3 H), 3.98 (s, 3 H), 4.00 (s, 3 H), 4.02 (s, 3 H), 6.73 (s, 1 H), 7.30–7.40 (m, 3 H), 7.61–7.70 (m, 2 H), 10.77 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 56.75 (q'), 57.09 (q'), 61.49 (q'), 62.47 (q'), 85.24 (s'), 98.25 (s'), 98.63 (d'), 105.77 (s'), 115.86 (s'), 116.57 (s'), 118.58 (s'), 123.51 (s'), 128.22 (d'), 131.65 (d'), 136.31 (s'), 146.03 (s'), 148.15 (s'), 152.40 (s'), 153.31 (s'); exact mass *m/z* calcd for $C_{22}H_{19}{}^{79}BrO_5$ 442.0416, found 442.0410. Anal. Calcd for $C_{22}H_{19}BrO_5$: C, 59.61; H, 4.33. Found: C, 59.64; H, 4.48.

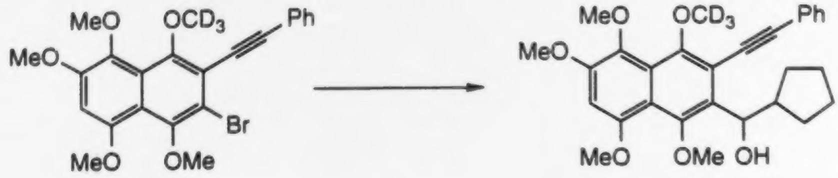
2-Bromo-1,5,6,8-tetramethoxy-4-(methoxy-d_3)-3-(phenylethynyl)naphthalene (200).



197 **198**

Methyl-d_3 *p*-toluenesulfonate[62] (1.22 g, 6.44 mmol) was tipped into a solution of naphthol **197** (1.425 g, 3.21 mmol) in dry DMF (20 mL), and NaH (60%w/w dispersion in oil, 0.24 g, 6.0 mmol) was then added. Stirring was continued at room temperature for 2.5 h. Saturated aqueous NH_4Cl (40 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 125 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated at room temperature, first under water-pump vacuum and then under oil pump vacuum (to remove DMF). Flash chromatography of the residue over silica gel (2.5 × 18 cm), using increasing amounts of EtOAc in hexane (from 30% to 40%), gave the deuterated ether **198** (1.32 g, 89%) as a pale yellow solid which was recrystallised from CH_2Cl_2–hexane to afford the pure material (1.21 g, 81%): mp 146–147 °C; FTIR ($CHCl_3$ cast) 1599, 1356, 1203, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 3 H), 3.86 (s, 3 H), 4.00 (s, 3 H), 4.02 (s, 3 H), 6.79 (s, 1 H), 7.34–7.44 (m, 3 H), 7.61–7.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 56.74 (q'), 57.36 (q'), 61.51 (q'), 62.10 (q'), 85.39 (s'), 98.24 (s'), 99.07 (d'), 114.57 (s'), 117.38 (s'), 118.59 (s'), 123.35 (s'), 125.34 (s'), 128.36 (d'), 128.59 (d'), 131.71 (d'), 137.07 (s'), 150.30 (s'), 150.77 (s'), 152.91 (s'), 154.38 (s'); exact mass *m/z* calcd for $C_{23}H_{18}D_3{}^{79}BrO_5$ 459.0761, found 459.0762.

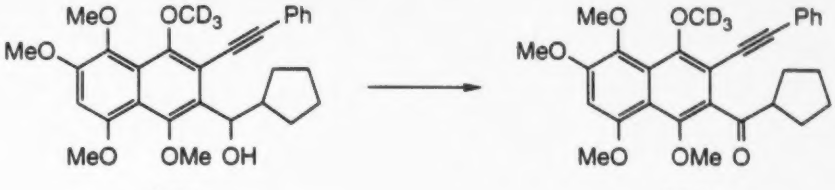
α-Cyclopentyl-1,5,6,8-tetramethoxy-4-(methoxy-d_3)-3-(phenylethynyl)-2-naphthalenemethanol (202).



198 **200**

n-BuLi (1.84 mL, 1.6 M in hexanes, 2.94 mmol) was added dropwise (*ca.* 1 min) to a stirred and cooled (-78 °C) solution of bromide **198** (679 mg, 1.47 mmol) in dry THF (16 mL). Halogen-metal exchange was monitored by TLC (silica, 1:1 EtOAc–hexane) and, after 5 min, a solution of freshly distilled cyclopentanecarboxaldehyde[69] **199** (363 mg, 3.70 mmol) in THF (2 mL plus 1 mL as a rinse) was injected rapidly. The brownish orange color of the solution faded within 30 sec. Stirring was continued at -78 °C for 20 min, and saturated aqueous NH_4Cl (20 mL) was added. The mixture was allowed to attain room temperature, and was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 20 cm), using increasing amounts of EtOAc in hexane (from 20% to 50%), gave alcohol **200** (621 mg, 88%) as a homogeneous [^{1}H NMR (200 MHz)], yellow foam: FTIR ($CHCl_3$ cast) 3550, 2951, 1601, 1381, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26–1.84 (m, 7 H), 1.92–2.14 (m, 1 H), 2.68–2.93 (m, 1 H), 3.59 (d, *J* = 11 Hz, 1 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 3.98 (s, 3 H), 4.02 (s, 3 H), 5.09 (t, *J* = 11 Hz, 1 H), 6.78 (s, 1 H), 7.35–7.45 (m, 3 H), 7.52–7.66 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.61 (t'), 29.28 (t'), 31.04 (t'), 46.98 (d'), 56.83 (q'), 57.12 (q'), 62.09 (q'), 63.30 (q'), 75.24 (d'), 85.16 (s'), 98.67 (d'), 99.43 (s'), 114.66 (s'), 116.82 (s'), 123.19 (s'), 125.47 (s'), 128.53 (d'), 128.64 (d'), 131.35 (d'), 131.56 (s'), 137.02 (s'), 150.38 (s'), 150.44 (s'), 153.12 (s'), 154.57 (s'); exact mass *m/z* calcd for $C_{29}H_{29}D_3O_6$ 479.2387, found 479.2390.

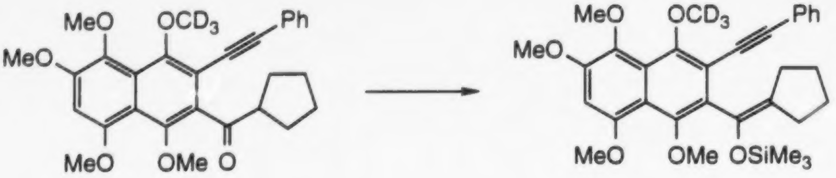
α-Cyclopentyl-1,5,6,8-tetramethoxy-4-(methoxy-d_3)-3-(phenylethynyl)-2-naphthalenylmethanone (204).



200 **201**

DDQ (836 mg, 3.7 mmol) was added to a stirred solution of alcohol **200** (883 mg, 1.8 mmol) in dry dioxane (20 mL). Stirring of the black suspension was continued at 100 °C overnight. The mixture was cooled, and 1:1 EtOAc–hexane (50 mL) was added. The mixture was filtered through a pad of aluminium oxide (neutral, grade III, 10 × 5 cm), the pad was washed with 1:1 EtOAc–hexane (2 L) and EtOAc (500 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 × 20 cm), using 1:5 EtOAc–hexane, gave impure material which was purified by flash chromatography over silica gel (2.5 × 20 cm), using first 1:1 CH_2Cl_2–petroleum ether and then 1:4:5 EtOAc–CH_2Cl_2–petroleum ether, to afford pure [^{1}H NMR (300 MHz)] ketone **201** (525 mg, 60%) as a yellow solid: FTIR ($CHCl_3$ cast) 2070, 1600, 1364, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46–1.62 (m, 2 H), 1.62–1.76 (m, 2 H), 1.76–1.91 (m, 2 H), 1.98–2.12 (m, 2 H), 3.48–3.60 (m, 1 H), 3.73 (s, 3 H), 3.83 (s, 3 H), 3.97 (s, 3 H), 3.98 (s, 3 H), 6.74 (s, 1 H), 7.28–7.37 (m, 3 H), 7.46–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 26.00 (t'), 29.15 (t'), 53.09 (d'), 56.71 (q'), 62.04 (q'), 64.11 (q'), 83.85 (s'), 97.65 (s'), 97.84 (d'), 112.58 (s'), 116.54 (s'), 123.14 (s'), 126.25 (s'), 128.30 (d'), 128.48 (d'), 131.52 (d'), 133.40 (s'), 136.89 (s'), 148.87 (s'), 151.11 (s'), 153.58 (s'), 153.98 (s'), 208.15 (s'); exact mass *m/z* calcd for $C_{29}H_{27}D_3O_6$ 477.2231, found 477.2229. A sample was recrystallized from CH_2Cl_2–petroleum ether: mp 109–111 °C.

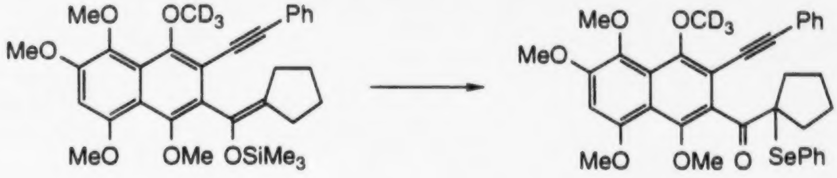
[Cyclopentylidene[1,5,6,8-tetramethoxy-4-(methoxy-d3)-3-(phenylethynyl)-2-naphthalenyl]methoxy]trimethylsilane (204).



201 **202**

Me_3SiOTf (0.50 mL, 2.66 mmol) was added to a stirred and cooled (0 °C) solution of ketone **201** (516 mg, 1.15 mmol) and dry Et_3N (1.0 mL, 7.17 mmol) in CH_2Cl_2 (30 mL). Stirring was continued at 0 °C for 2 h. Saturated aqueous $NaHCO_3$ (30 mL) was added, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). All combined organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 20 cm), using increasing amounts of EtOAc in hexane (from 15% to 20%), gave the silyl enol ether **202** (525 mg, 88%) as a pale yellow, homogeneous [^{1}H NMR (200 MHz)] solid: FTIR ($CHCl_3$ cast) 2070, 1800, 1363, 1341, 1050, 876, 848 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 9 H), 1.48–1.73 (m, 4 H), 1.80–1.92 (m, 1 H), 2.26–2.65 (m, 3 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 3.93 (s, 3 H), 3.97 (s, 3 H), 6.72 (s, 1 H), 7.25–7.37 (m, 3 H), 7.45–7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 0.89 (q'), 26.61 (t'), 27.26 (t'), 29.25 (t'), 30.13 (t'), 56.79 (q'), 57.44 (q'), 62.06 (q'), 62.37 (q'), 86.18 (s'), 96.16 (s'), 98.64 (d'), 116.95 (s'), 117.63 (s'), 124.03 (s'), 125.91 (s'), 126.30 (s'), 128.12 (d'), 128.35 (d'), 129.48 (s'), 131.57 (d'), 136.31 (s'), 136.95 (s'), 150.49 (s'), 151.53 (s'), 153.57 (s'), 153.84 (s'); exact mass *m/z* calcd for $C_{32}H_{35}D_3O_6Si$ 549.2625, found 549.2622. A sample was recrystallized from CH_2Cl_2–petroleum ether: mp 175–177 °C.

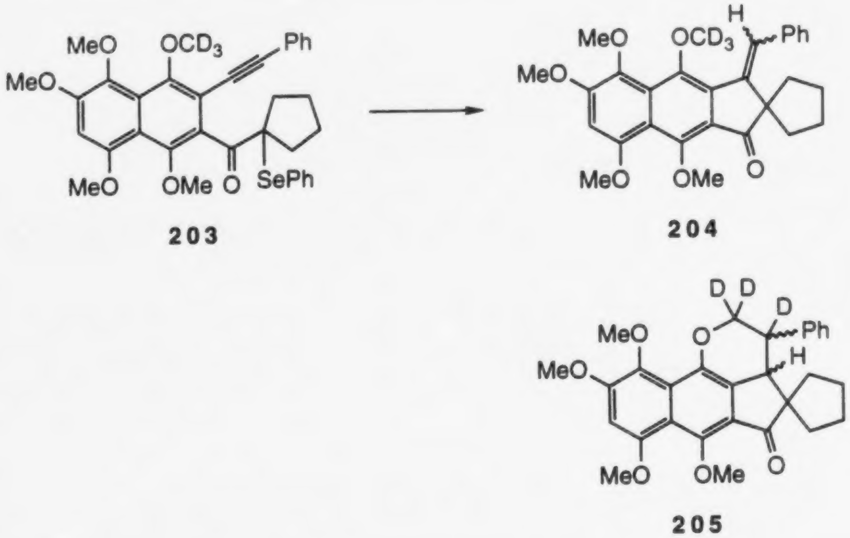
[1-(Phenylseleno)cyclopentyl][1,5,6,8-tetramethoxy-4-(methoxy-d_3)-3-(phenylethynyl)-2-naphthalenyl]methanone (205).



202 **203**

PhSeCl (211 mg, 1.10 mmol) was tipped into a stirred and cooled (-78 °C) solution of silyl enol ether **202** (484 mg, 0.88 mmol) in dry THF (16 mL). Stirring was continued at -78 °C for 1 h. The cooling-bath was removed, and stirring was continued for 2 h. CH_2Cl_2 (1 × 100 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ (1 × 50 mL), and water (1 × 50 mL). The organic layer was dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 15 cm), using 1:3 EtOAc–petroleum ether, gave the phenylseleno ketone **203** (506 mg, *ca.* 91%) as a orange foam containing trace impurities (TLC, silica, 1:1 EtOAc–hexane) but suitable for the next stage: FTIR ($CHCl_3$ cast) 2070, 1800, 1363, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64–1.79 (m, 2 H), 1.80–2.05 (m, 4 H), 2.23–2.38 (m, 2 H), 3.74 (s, 3 H), 3.87 (s, 3 H), 3.98 (s, 3 H), 4.02 (s, 3 H), 6.79 (s, 1 H), 7.22–7.37 (m, 6 H), 7.44–7.57 (m, 2 H), 7.72–7.78 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 24.33 (t'), 36.82 (t'), 56.79 (q'), 57.12 (q'), 62.13 (q'), 63.43 (q'), 65.57 (s'), 84.65 (s'), 97.92 (s'), 98.40 (d'), 113.21 (s'), 116.63 (s'), 123.24 (s'), 126.24 (s'), 128.27 (d'), 128.46 (d'), 128.52 (d'), 128.66 (d'), 129.52 (s'), 131.65 (d'), 131.85 (s'), 137.01 (s'), 137.65 (s'), 148.71 (s'), 151.15 (s'), 153.70 (s'), 154.25 (s'), 206.16 (s'); exact mass *m/z* calcd for $C_{35}H_{31}D_3O_6{}^{80}Se$ 633.1708, found 633.1694.

5,6,8,9-Tetramethoxy-4-(methoxy-d_3)-3-(phenylmethylene)spiro[2*H*-benz[*f*]indene-2,1'-cyclopentan]-1(3*H*)-one (204) and 3,3a-Dihydro-6,7,9,10-tetramethoxy-3-phenylspiro[4*H*-benz[5,6]indeno[7,1-*bc*]pyran-4,1'-cyclopentan]-5(2*H*)-one-2,2,3-d_3 (205).



203

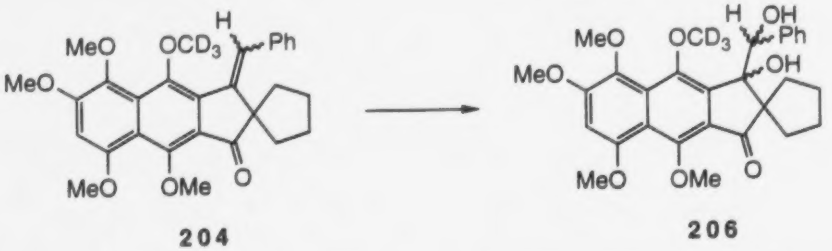
204

205

AIBN (2 mg) was added to a solution of selenide **203** (170 mg, 0.27 mmol) in dry PhH (4.0 mL), and the mixture was lowered into an oil-bath set at 80 °C. As soon as refluxing began, a solution of Ph_3SnH (151 mg, 0.52 mmol) in dry PhH (0.5 mL plus 2 × 0.3 mL as a rinse) was injected rapidly. Stirring was continued at 80 °C overnight, and then the mixture was cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (2.5 × 15 cm), using mixtures of EtOAc–CH_2Cl_2–petroleum ether (from 1:1:9 to 1:1:3), gave olefinic ketone **204** (96.5 mg, 75%) as a yellow foam and abstraction product **205** (5.5 mg, 4%) as a pale yellow foam. Compound **204** was a mixture of two isomers [^{1}H NMR (200 MHz)] and had: FTIR ($CHCl_3$ cast) 1709, 1366, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38–1.50 (m, 1 H), 1.75–2.07 (m, 6 H), 2.12–2.25 (m, 1 H), 3.59 (s, 1.14 H), 3.86 (s, 1.86 H), 3.97 (s, 1.86 H), 4.00 (s, 1.14 H), 4.01 (s, 3 H), 4.05 (s, 1.86 H), 4.07 (s, 1.14 H), 6.69 (s, 0.38 H), 6.74 (s, 0.38 H), 6.75 (s, 0.62 H), 7.13–7.42 (m, 5 H), 8.30 (s, 0.62 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 26.97 (t'), 27.06 (t'), 56.62 (q'), 57.40 (q'), 60.24 (s'), 62.15 (q'), 62.48 (q'), 62.79 (q'), 63.39 (q'), 65.40 (s'), 97.53 (d'), 97.78 (d'), 118.00 (s'), 121.24 (s'), 124.61 (s'), 126.59 (d'), 126.80 (d'), 127.09 (d'), 128.04 (d'), 128.23 (d'), 128.63 (d'), 128.97 (d'), 130.60 (d'), 133.70 (s'), 134.75 (s'), 137.08 (s'), 137.70 (s'), 138.26 (s'), 139.12 (s'), 141.81 (s'), 142.58 (s'), 147.82 (s'), 148.13 (s'), 152.77 (s'), 152.83 (s'), 153.79 (s'), 156.66 (s'), 156.70 (s'), 204.09 (s'), 206.90 (s'); exact mass *m/z* calcd for $C_{29}H_{27}D_3O_6$ 477.2231, found 477.2209.

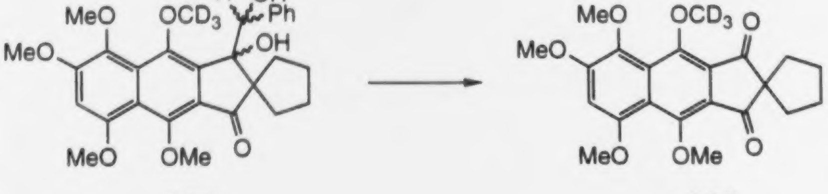
Abstraction product **205** consisted of a mixture of two isomers [^{1}H NMR (200 MHz)] and had: FTIR ($CHCl_3$ cast) 2933, 1708, 1599, 1365, 1051, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.75–1.10 (m, 2 H), 1.17–1.41 (m, 3 H), 1.49–1.79 (m, 3 H), 1.82–2.22 (m, 1 H), 3.70–4.01 (eight singlets, 12 H), 6.59 (s, 0.65 H), 6.70 (s, 0.35 H), 6.97–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.15 (t'), 25.29 (t'), 25.77 (t'), 26.04 (t'), 32.99 (t'), 33.13 (t'), 33.91 (t'), 38.39 (t'), 46.08 (d'), 47.43 (d'), 57.24 (q'), 57.37 (q'), 62.05 (q'), 62.47 (q'), 62.61 (s'), 63.16 (s'), 63.22 (q'), 63.46 (q'), 98.34 (d'), 98.43 (d'), 117.91 (s'), 118.10 (s'), 121.23 (s'), 121.48 (s'), 125.78 (s'), 126.98 (d'), 127.45 (d'), 127.72 (s'), 128.17 (d'), 128.43 (d'), 128.95 (d'), 130.09 (d'), 137.86 (s'), 139.27 (s'), 140.95 (s'), 143.10 (s'), 143.66 (s'), 150.18 (s'), 150.53 (s'), 152.45 (s'), 156.60 (s'), 156.73 (s'), 206.55 (s'), 207.19 (s'); exact mass *m/z* calcd for $C_{29}H_{27}D_3O_6$ 477.2231, found 477.2231.

3-Hydroxy-3-(hydroxyphenylmethyl)-5,6,8,9-tetramethoxy-4-(methoxy-d_3)spiro[2*H*-benz[*f*]indene-2,1'-cyclopentane]-1(3*H*)-dione (206).



A freshly prepared solution of OsO_4 in bench pyridine (4.1 mL, 11.3 mg per mL, 0.107 mmol of OsO_4) was added with stirring to the radical cyclization products **204** (49.2 mg, 0.103 mmol). Stirring was continued at room temperature for 1 h. The mixture was then diluted with EtOAc (50 mL) and was washed with 10 % aqueous sodium bisulfite (2 × 25 mL), 2 N aqueous HCl (1 × 25 mL), and water (1 × 25 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 2:3 EtOAc–hexane, gave the required diols **206** as a yellow, glassy solid (42.9 mg, 81%) which was a mixture of two isomers: FTIR (CH_2Cl_2 cast) 3475, 2947, 1719, 1599, 1382, 1350 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55–2.45 (m, 9 H), 3.35–4.10 (nine singlets corresponding to 12 H), 4.36 (br s, 0.6 H), 4.75 (br s, 0.4 H), 4.96 (br d, J = 8.0 Hz, 0.4 H), 5.01 (br s, 0.6 H), 6.65–7.25 (m including a singlet at δ 6.75, 6 H); ^{13}C NMR ($CHCl_3$, 75.469 MHz) δ 25.42 (t'), 25.68 (t'), 26.86 (t'), 27.31 (t'), 27.62 (t'), 27.75 (t'), 35.88 (t'), 37.69 (t'), 56.61 (q'), 57.31 (q'), 57.38 (q'), 62.32 (q'), 62.46 (q'), 63.25 (q'), 63.47 (q'), 66.66 (s'), 67.49 (s'), 78.58 (d'), 80.11 (d'), 84.56 (s'), 85.11 (s'), 97.47 (d'), 97.54 (d'), 117.89 (s'), 118.23 (s'), 123.45 (s'), 124.33 (s'), 127.40 (d'), 127.45 (d'), 127.62 (d'), 127.75 (d'), 127.81 (d'), 127.89 (d'), 128.20 (s'), 128.99 (s'), 135.10 (s'), 136.16 (s'), 137.04 (s'), 138.69 (s'), 140.28 (s'), 152.30 (s'), 152.81 (s'), 156.77 (s'), 156.84 (s'), 200.39 (s'), 201.37 (s'); exact mass *m/z* calcd for $C_{29}H_{29}D_3O_8$ 511.2285, found 511.2296.

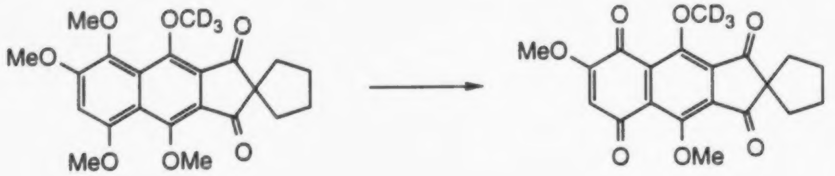
5,6,8,9-Tetramethoxy-4-(methoxy-d_3)spiro[2*H*-benz[*f*]indene-2,1'-cyclopentane]-1,3-dione (207).



206 **207**

H_5IO_6 (55 mg, 0.24 mmol) was added in one batch to a stirred solution of diols **206**(37.5 mg, 0.073 mmol) in MeOH (3.0 mL). After stirring at room temperature for 2 h [TLC control, silica, EtOAc–hexane (1:3)], the mixture was diluted with EtOAc (50 mL), washed with water (1 × 30 mL), and dried ($MgSO_4$). [The reaction must be stopped as soon as it is complete otherwise the yield is lower.] Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 8 cm), using 1:3 EtOAc–hexane, gave spirodiketone **207** (20.7 mg, 69%) as a homogeneous [^1H NMR (200 MHz)] yellow oil: FTIR ($CHCl_3$ cast) 1729, 1701, 1596, 1356 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.96–2.06 (m, 8 H), 3.88 (s, 3 H), 4.03 (s, 6 H), 4.06 (s, 3 H), 6.90 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 28.15 (t'), 36.56 (t'), 57.13 (q'), 58.03 (q'), 62.79 (q'), 62.99 (s'), 63.60 (q'), 100.48 (d'), 121.70 (s'), 124.75 (s'), 127.82 (s'), 131.55 (s'), 139.91 (s'), 154.08 (s'), 154.14 (s'), 157.38 (s'), 202.45 (s'), 203.86 (s'); exact mass *m/z* calcd for $C_{22}H_{21}D_3O_7$ 403.1710, found 403.1705.

6,9-Dimethoxy-4-(methoxy-d_3)spiro[2*H*-benz[*f*]indene-2,1'-cyclopentane]-1,3,5,8-tetrone (208).

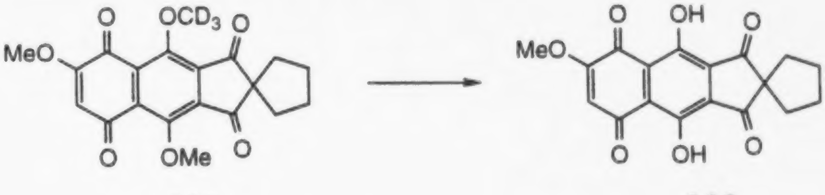


207 **208**

A solution of CAN (85.9 mg, 0.157 mmol) in water (1.0 mL) was added quickly to a stirred solution of spirodiketone **207** (23.4 mg, 0.058 mmol) in CH_3CN (2.0 mL). Stirring was continued at room temperature for 10 min [TLC control, silica, EtOAc–hexane (2:3)]. EtOAc (50 mL) was added, and the mixture was washed with water (2 × 25 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using 2:3 EtOAc–hexane, gave quinone **208** (16.9 mg, 78%) as homogeneous [TLC, silica, EtOAc–hexane (2:3)] yellow crystals: mp 164–175 °C; FTIR ($CHCl_3$ cast) 2880, 2080, 1713, 1686, 1653, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.98 (br s, 8 H), 3.89 (s, 3 H), 4.06 (s, 3 H), 6.14 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 27.48 (t'), 35.84 (t'), 56.67 (q'), 61.37 (s'), 63.35 (q'), 110.76 (d'), 131.56 (s'), 132.46 (s'), 138.46 (s'), 139.72 (s'), 153.46 (s'), 154.15 (s'), 160.03 (s'), 178.31 (s'), 182.61 (s'), 200.76 (s'), 200.82 (s'); exact mass *m/z* calcd for $C_{20}H_{15}D_3O_7$ 373.1241, found 373.1236.

4,9-Dihydroxy-6-methoxyspiro[2*H*-benz[*f*]indene-2,1'-cyclopentane]-1,3,5,8-tetrone (209)

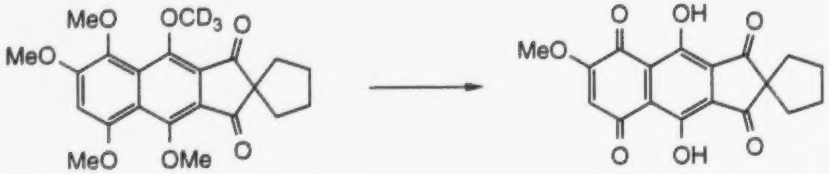
(a) By demethylation of (208).



208 **209**

BBr_3 (180 µL, 1.75 M in CH_2Cl_2, 0.32 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of quinone **208** (12.3 mg, 0.033 mmol) in dry CH_2Cl_2 (2.0 mL). The solution became deep red during the addition. Stirring at -78 °C was continued for 2 h after the addition. Water (20 mL) and CH_2Cl_2 (20 mL) were then added, and the mixture was allowed to separate into two phases. The organic layer was washed with 10%v/v HCl (1 × 20 mL) and water (1 × 20 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using 100:50:0.5 CH_2Cl_2–EtOAc–AcOH, gave the crude product (8.9 mg). This was dissolved at room temperature in CH_2Cl_2, diluted with EtOAc, and allowed to stand for 24 h. Crystals of pure [TLC, silica, CH_2Cl_2–EtOAc–AcOH (100:50:1)] quinone **209** (7.6 mg, 68%) were obtained, identical to a sample made in the non-deuterated series. ^1H NMR (300 MHz, $CDCl_3$) 1.91–2.06 (m, 8 H), 3.99 (s, 3 H), 6.28 (s, 1 H), 12.50 (s, 1 H), 13.15 (s, 1 H); ^{13}C NMR (75.469 MHz) 27.37, 35.70, 57.32, 60.91, 111.05, 117.66, 117.78, 135.49, 137.28, 152.77, 153.59, 161.16, 183.38, 188.64, 201.07, 201.13; exact mass *m/z* calcd for $C_{18}H_{14}O_7$, 342.0739, found 342.0734.

(b) By demethylation of 207.



207 **209**

BBr_3 (1.75 M in CH_2Cl_2, 150 μL, 0.26 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of spirodiketone **207** (5.5 mg, 0.014 mmol) in dry CH_2Cl_2 (1.0 mL). The solution became deep red during the addition. Stirring was continued at -78 °C for 2 h after the addition. Water (20 mL) and CH_2Cl_2 (20 mL) were then added, and the mixture was allowed to separate into two phases. The organic layer was washed with 10%v/v HCl (1 × 20 mL) and water (1 × 20 mL), dried (Na_2SO_4) and evaporated. The residue was dissolved in $CHCl_3$ (2 mL) that had been shaken with concentrated HCl. The solution was stirred for 24 h and then evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using 100:50:0.5 CH_2Cl_2–EtOAc–AcOH, gave quinone **211** (2.9 mg, 63 %), identical to material made by the two-step route.

IV REFERENCES AND FOOTNOTES

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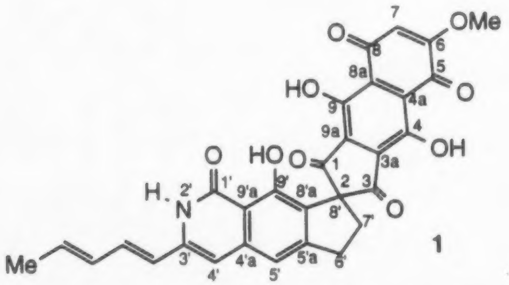

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Part 2

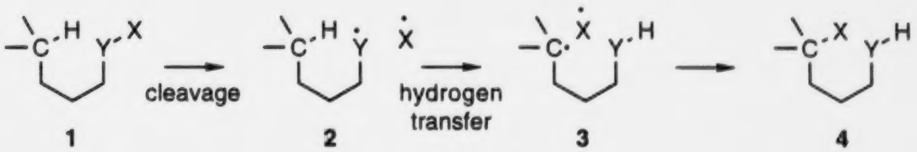
USE OF INTRAMOLECULAR HYDROGEN ABSTRACTION IN ORGANIC SYNTHESIS

I INTRODUCTION

General Background

Free radicals can undergo a variety of rearrangements,[1] and amongst them, the radical ring closure has evolved into a useful tool in organic synthesis, especially for the construction of carbocyclic molecules.[2] This radical rearrangement has been the pivotal element in synthesis of molecular structures having a high degree of complexity.

A second rearrangement of free radicals which is receiving renewed attention is the intramolecular hydrogen shift (Scheme 1). In this method, functionalization of an unactivated carbon atom is achieved by intramolecular abstraction (**2**→**3**) of a hydrogen atom by a radical located on a remote functional group (Y).



1 **2** **3** **4**

or other reactions

$Y = O$ $X = NO, OH, Cl, Br, I, Pb(OAc)_3$
$Y = N$ $X = I$
$Y = N^+$ $X = Cl, Br$
$Y = C$ $X = Br, I, SePh$

Scheme 1

Most examples reported are characterized by the use of reactive radicals ($Y^{\cdot}$) centered on heteroatoms, often oxygen or nitrogen, or by radicals on carbon. These radicals are generated by homolytic cleavage of the Y–X bond (**1**→**2**), either thermally, photochemically, or by using specific chemical methods.

The translocated radical **3** can either recombine with radical X· to give product **4** (as shown), or undergo another radical rearrangement. The outcome of the second rearrangement will largely depend on both the reaction conditions and the molecular structure of the substrate.

The development of new synthetic methodologies based on intramolecular hydrogen shift is attractive, since this radical rearrangement generally exhibits a preference for 1,5-hydrogen transfers. Such selectivity was first attributed to the quasi linear arrangement of the three atoms involved in the transition state. More recently, energy calculations[3] suggest that this preference for the 6-membered transition state originates from the favorable entropy of activation. These calculations also show that a slight distortion in the colinearity of the participating atoms (up to 35°) has no dramatic effect on the transition state energy. Although the 7-membered ring transition state offers better colinearity, the intramolecular ring interactions favor the lower energy 1,5-hydrogen transfer.

Another requirement of intramolecular hydrogen abstraction is the relative proximity of the radical and the hydrogen atom involved in the transfer. In steroid examples, the most effective distance was evaluated to be 2.5–2.7 Å.[4]

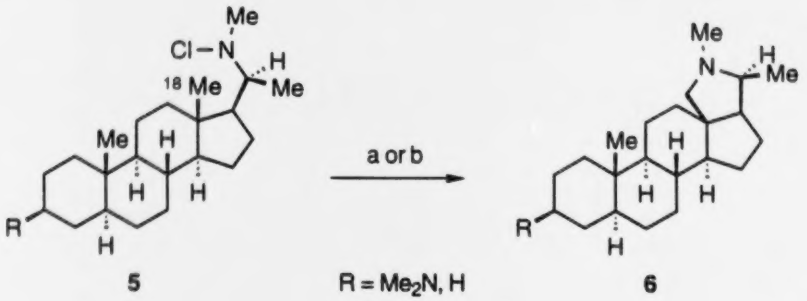
The following literature survey of intramolecular hydrogen transfers will be divided in five sections, each focussing on the species performing the radical abstraction: heteroatom radicals, vinyl radicals, acyl radicals, aryl radicals, and finally, alkyl radicals. The emphasis will be on the synthetic utility of these rearrangements.

Intramolecular Hydrogen Abstraction by Heteroatom Radicals

Nitrogen and oxygen centered radicals constitute the bulk of examples found in this category. Radicals located on these heteroatoms are generally very reactive. Therefore, they are efficient in 1,5-hydrogen transfer processes.

Remote functionalization by hydrogen abstraction gained importance at the end of the 1950s in the derivatization of steroids, chemical agents essential for the maintenance of many biological functions in animals and humans.

In the Hofmann–Löffler–Freitag reaction,[5] the intramolecular hydrogen abstraction is performed by the nitrogen radical [Y = N, N$^+$; X = Cl, Br, Scheme 1].[6] This reaction was mainly used for construction of pyrrolidines from acyclic amines, and two independent groups[7,8] have demonstrated its utility in the remote functionalization of the 18-methyl group of the steroid skeleton (Scheme 2). For example, Corey[7] completed the synthesis of dihydroconessine **6** (R = Me_2N) using this reaction.

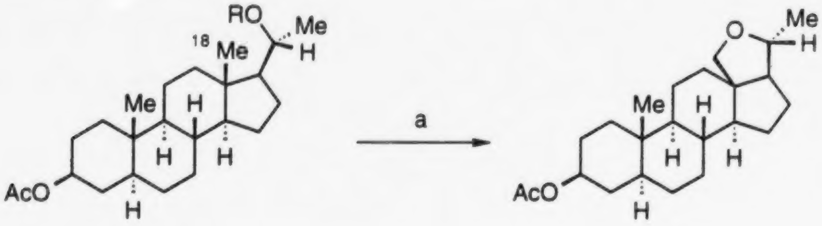


Scheme 2 *Reagents and conditions:* (a) *hv*, 90% H_2SO_4, 0 °C, 70 min, 79% (R = Me_2N) (reference 7b); (b) conc. H_2SO_4, AcOH (reference 8)

Both 1,4- and 1,5-hydrogen abstraction in *N*-halogeno-amides[9,10] have been reported, the latter being used in the synthesis of 5-membered lactones. Carbamoyl radicals[11] have also been used to initiate intramolecular hydrogen transfer. In these ambident radicals, the nitrogen radical is responsible for hydrogen abstraction.

A large number of intramolecular transfers involving alkoxy radicals have been reported.[4,12] This radical rearrangement dominated the chemistry of steroids for many years, and several convenient methods for the generation of the heteroatom radical have been developed.

The alkoxy radical precursors can be obtained by simple treatment of alcohol functional groups with lead tetraacetate.[4, 13] The weak Pb–O bond of the resulting lead(IV) alkoxide [Y = O; X = $Pb(OAc)_3$, Scheme 1] is easily cleaved, and the products of the subsequent radical rearrangement are cyclic ethers, lactols or lactones (or mixtures of these)[6]. The following example shows the use of this method in functionalization of the 18-methyl group of a steroid[14] (Scheme 3).



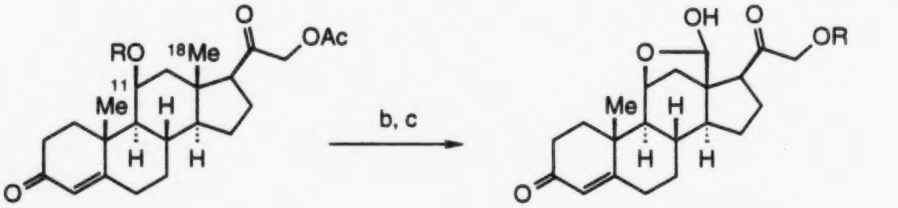
7 R = H
8 R = Pb(OAc)$_3$

9

Scheme 3 *Reagents and conditions:* (a) Pb(OAc)$_4$, PhH, reflux, 25% (R = H) (reference 14)

The involvement of D. H. R. Barton[15] in this radical chemistry had an impressive impact on the development of remote functionalization by intramolecular hydrogen abstraction. Photochemically induced decomposition of nitrites [Y = O, X = NO, Scheme 1] was the method used to generate the alkoxy radical.[6] In the first example reported,[16] functionalization of the 18-methyl group was achieved from the 20-hydroxy group in 34 % yield (the substrate was similar to compound **7**, R = NO, Scheme 3).

By this method, Barton and Beaton[17] realized a short synthesis of aldosterone **13** (Scheme 4). Functionalization of the 18-methyl group was achieved by the 11-β hydroxyl



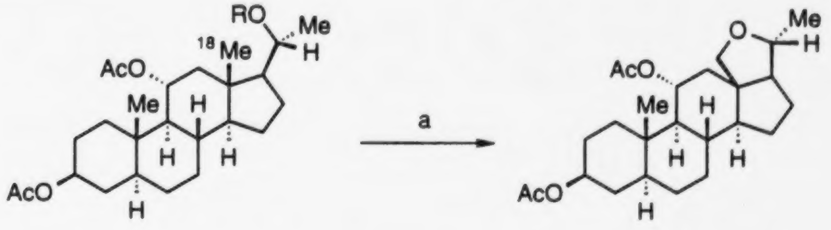
a **10** R = H
11 R = NO

d **12** R = Ac
13 R = H (+)-ALDOSTERONE

Scheme 4 *Reagents and conditions:* (a) ClNO, pyridine, rt; (b) *hv*, PhMe, 32 °C, 35 min, 15% (over two steps); (c) NaNO$_2$, AcOH, H$_2$O, 10 °C, 5 min, 66%; (d) K$_2$CO$_3$, MeOH, H$_2$O, CH$_2$Cl$_2$, rt, 5 min, 44% (reference 17b)

radical of corticosterone 21-acetate (**11**, R = ·) obtained during photolysis of nitrite **11**. The intermediate oxime (not shown) was hydrolyzed to the corresponding lactol **12**, and removal of the acetate by catalytic base hydrolysis completed the concise synthesis. Other methods for the construction of aldosterone **13** developed at the time were much more laborious.[18]

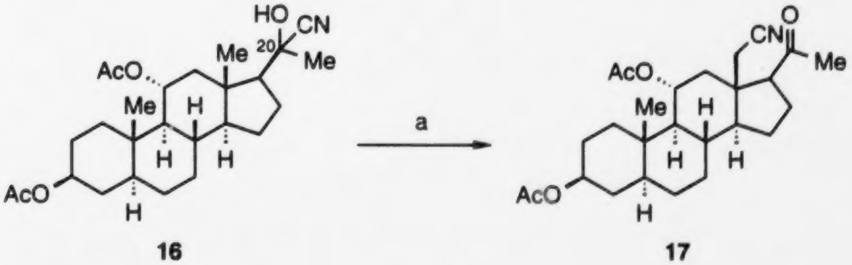
Alkoxy radicals were also generated by cleavage of hypohalogenites[15b,15d] [Y = O, X = Cl,[19] Br,[20] I,[4, 21] Scheme 1]. Although comparable results were obtained with the various halogens, the decomposition of the hypoiodite, formed *in situ* by treatment of a refluxing solution of the alcohol with lead tetraacetate in the presence of iodine, appeared to be the method of choice. For example,[22] the 18-methyl group of compound **14** was functionalized in this way, and cyclic ether **15** was isolated (Scheme 5).



14 **15**

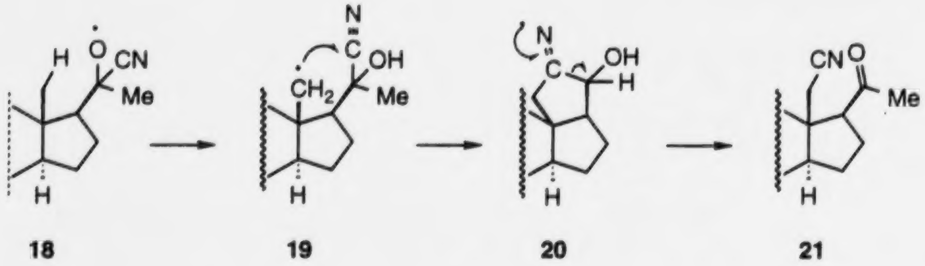
Scheme 5 *Reagents and conditions:* (a) Pb(OAc)$_4$, I$_2$, CaCO$_3$, cyclohexane, reflux, 19 h, 23 % (R = H) (reference 22b)

In the same communication,[22] a 1,4-nitrile migration from a cyanohydrin group



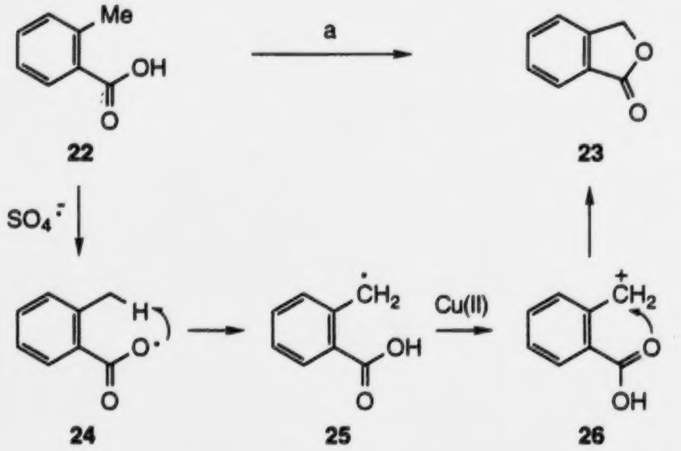
16 **17**

Scheme 6 *Reagents and conditions:* (a) Pb(OAc)$_4$, CaCO$_3$, I$_2$, cyclohexane, reflux, 3.5 h, 55-60% (reference 23a) (position 20) to the unactivated 18-methyl group of the steroid (oxidative cyanohydrin-cyano-ketone rearrangement) was also reported (Scheme 6). The mechanism[23] of this unique radical rearrangement was investigated further (Scheme 7). After the oxygen radical has abstracted hydrogen from the 18-methyl group (**18→19**), the primary alkyl radical **19** adds to the cyano group in a 5-*exo-dig* fashion, leading to the formation of pentacyclic intermediate **20**, which undergoes a β-fragmentation (**20→21**) to give the observed ketone **21** after oxidation.



Scheme 7

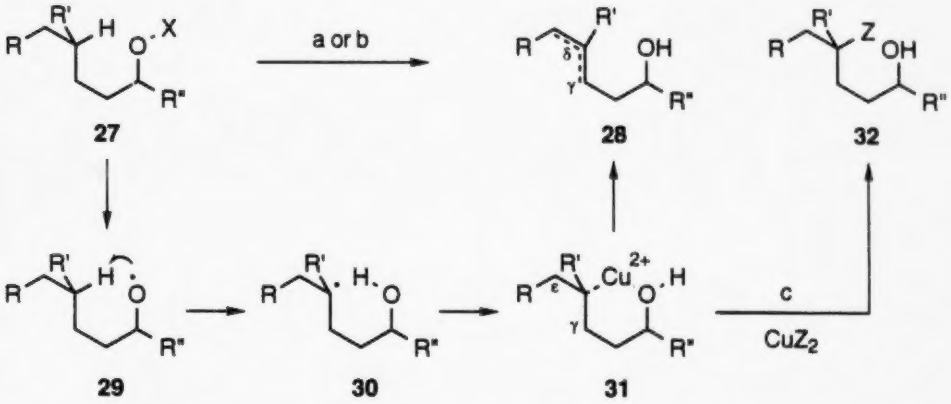
Another oxygen centered radical capable of hydrogen abstraction is the acyloxy



Scheme 8 *Reagents and conditions:* (a) $Na_2S_2O_8$, cat. $AgNO_3$, cat. $CuCl_2$, CH_3CN/H_2O (1:1), 80 °C, 56% (reference 25)

radical. In earlier studies of substituted benzene rings,[24] it was concluded that hydrogens were abstracted from the *ortho* substituents of an acyloxy radical, and that the transfer was indeed intramolecular. Based on this reaction, Surzur[25] recently suggested a method for the synthesis of lactones (Scheme 8). In these examples, activation of the hydrogen, caused by an adjacent olefin, aryl group, or carbonyl group, is necessary in order for the less reactive acyloxy radical to initiate the radical shift.

Remote introduction of a double bond[28] was achieved by means of a 1,5-hydrogen abstraction by an oxygen radical (Scheme 9). Two experimental procedures were



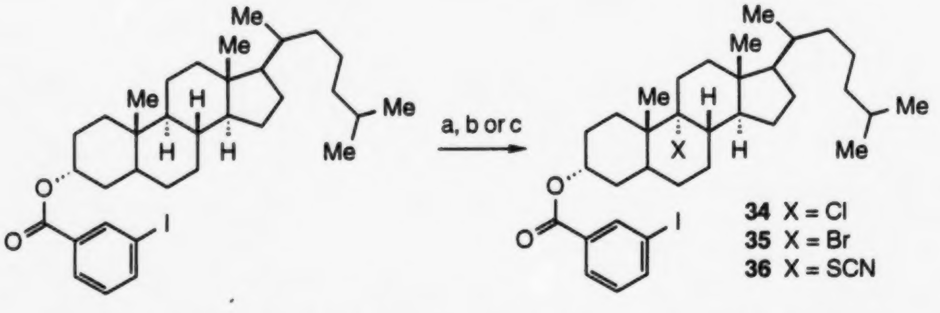
Scheme 9 *Reagents and conditions:* (a) $FeSO_4$, $CuSO_4$, AcOH, H_2O, rt, overnight, 73% (R = Me, R' = R" = H; δ/γ ≈ 3.3:1); (b) $Cu(OAc)_2$, *hv*, ≈10 °C, 5–6 h, 32% (R = Me, R' = R" = H; δ/γ ≈ 5.4:1); (c) $FeSO_4$, CuZ_2, CH_3CN, H_2O, rt, 5–8 h, 65% (R = Me, R' = R" = H, Z = Cl) (reference 28b)

developed for this transformation. Decomposition of an alkyl hydroperoxide[28a,28b] [Y = O, X = OH, Scheme 1] by ferrous sulfate (*e.g.* Fenton's reaction) produced alkoxy radical **29**, which then abstracted a hydrogen atom from the carbon chain (**29**→**30**). At this stage, the translocated radical **30** was oxidized by the copper reagent to give carbocation **31**. Elimination of either the γ or ε proton introduced the γ- or δ–double bond respectively, the latter usually being the major compound isolated.

In the second procedure,[28c] Barton's irradiation of nitrites **27** [Y = O, X = NO, Scheme 1] was used to generate the alkoxy radical. The translocated radical **30** was quenched by cupric acetate, and the intermediate was decomposed by a similar pathway. In general, a lesser amount of the desired products was formed using these conditions.

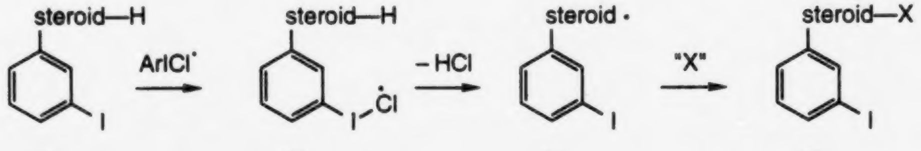
In another variation[29] of this method, different cupric reagents CuZ_2 (Z = Cl, Br, I, SCN, or N_3) were used in the capture of rearranged radical **30** (Scheme 9), and a variety of compounds **32** (Z = Cl, Br, I, SCN, or N_3) were synthesized.

The various examples described so far in this introduction have in common the use of 1,5-hydrogen transfers to functionalize unactivated carbons. Breslow[30] developed a method based on distant hydrogen abstraction (Scheme 10), and also found some applications in steroid chemistry. A functional group, capable of momentarily carrying a chlorine radical (**37**→**38**, Scheme 11), is attached to the steroid skeleton. This group is usually an ester substituted by a heteroatom (iodine in this example).



34 X = Cl
35 X = Br
36 X = SCN

Scheme 10 *Reagents and conditions:* (a) *p*-NO_2PhICl_2, *hv*, CH_2Cl_2, 90%; (b) *p*-NO_2PhICl_2, 20 equiv of CBr_4, *hv*, CH_2Cl_2, *ca.* 83%; (c) $PhICl_2$, 11 equiv of $(SCN)_2$, CH_2Cl_2, 0 °C, 64% (reference 30b)



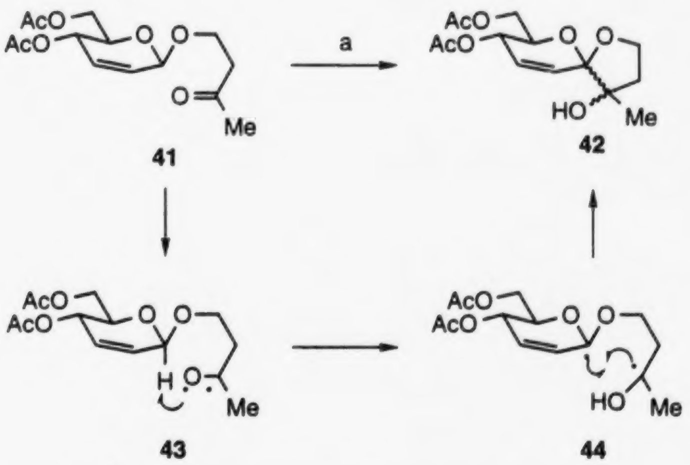
37 **38** **39** **40**

Scheme 11

A specific hydrogen transfer occurs (**38→39**), and the carbon radical is captured by the additive 'X', to give compounds **34–36**, along with elimination products (not shown).

With the exception of the radical rearrangement of cyanohydrins (Schemes 6 and 7), the formation of new C–C bonds has not yet been mentioned, and the next examples will describe this important reaction.

Photochemical excitation of carbonyl groups[31] generates an excited state (triplet) which can potentially be used in hydrogen abstraction. This principle was applied recently in the formation of spirocarbohydrates[32] **42** (Scheme 12). In the best-yielding example,

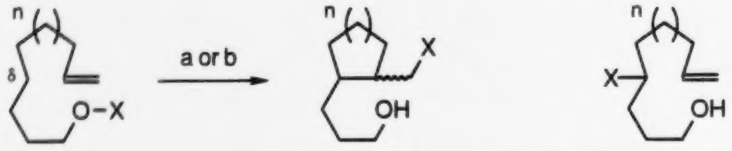


Scheme 12 *Reagents and conditions:* (a) *hv*, PhH, 43% (combined yield) (reference 32b)

irradiation of ketone **41** led to formation of diradical **43**. An allylic hydrogen, also at the anomeric position of the carbohydrate, was abstracted by the excited state of the ketone, and the two carbon radicals of intermediate **44** were recombined to give alcohols **42** as a mixture of all possible isomers.

This photochemical rearrangement was also used in the synthesis of a steroid[33] and of tetracycline,[34] and in the construction of the spiro center of fredericamycin A.[35] More recently, Kraus and Wu[36] observed a very unusual 1,9-hydrogen abstraction during photochemical excitation of an α-ketoester, and 8-membered lactones were isolated as products of the radical rearrangement.

Cekovic and Ilijev[37] constructed 5-membered and 6-membered carbocycles from translocated radicals (Scheme 13). The translocated radical at position δ, obtained via hydrogen abstraction by the alkoxy radical, either added to the double bond to form cyclic compounds **46a–d,** or was trapped directly by the counter radical to produce compounds **47a–d**.



45a X = NO, n = 1
45b X = NO, n = 2
45c X = Cl, n = 1
45d X = Cl, n = 2

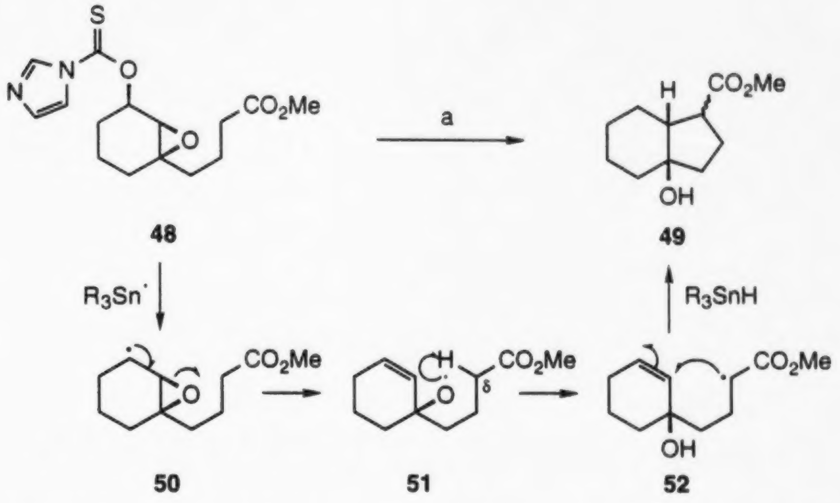
46a X = NO, n = 1 (32%)
46b X = NO, n = 2 (25%)
46c X = Cl, n = 1 (25%)
46d X = Cl, n = 2 (29%)

47a X = NO, n = 1 (14%)
47b X = NO, n = 2 (14%)
47c X = Cl, n = 1 (19%)
47d X = Cl, n = 2 (16%)

Scheme 13 *Reagents and conditions:* (a) *hν*, PhH, (X = NO); (b) Fe^{2+}, CCl$_4$ (0.025 M) (X = Cl) (reference 37)

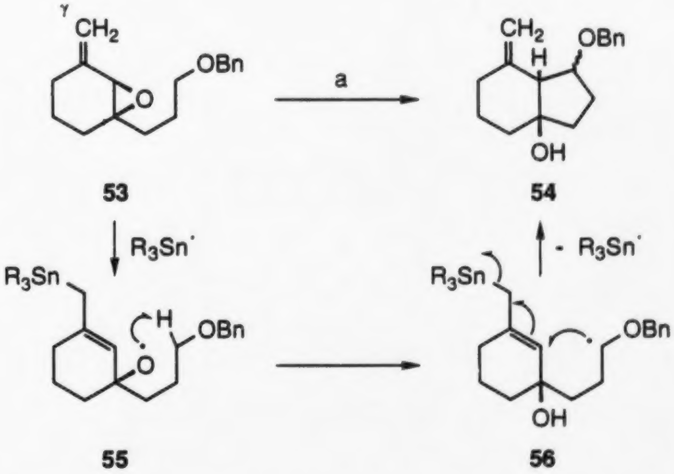
Esker and Newcomb[38] also used a similar strategy in the formation of carbocyclic compounds from radical cyclization of a translocated radical α to a carbonyl group, itself obtained from hydrogen abstraction by an acyloxy radical (not shown).

In another synthetically useful methodology for production of carbocyclic compounds, alkoxy radicals were generated by radical ring opening[39] (**50→51**) (Scheme 14). In this strategy, the allyl alkoxy radical **51** abstracted a δ hydrogen, leading to the formation of carbon radical **52**. The translocated radical is appropriately placed for 5-*exo-trig* cyclization onto the double bond (**52→49**) which was formed during the initial fragmentation step (**50→51**). This method is particularly useful for construction of bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane skeletons.



Scheme 14 *Reagents and conditions:* (a) *n*-Bu_3SnH, AIBN, PhH, reflux, 68% (reference 39)

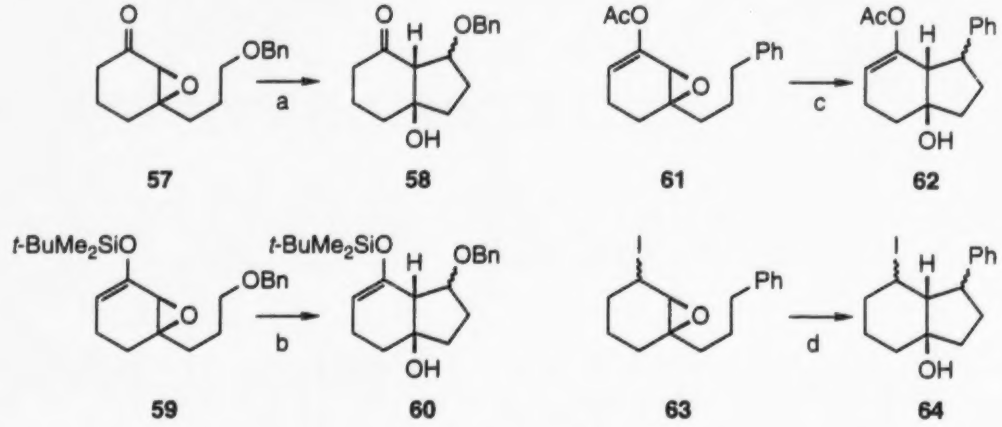
In a variation of this methodology for the formation of bicyclic compounds,[40] a catalytic radical source was used (Scheme 15). Rearrangement of an allylic epoxide into an allylic alkoxy radical (**53**→**55**) was initiated by addition of stannane radical to the γ



Scheme 15 *Reagents and conditions:* (a) 0.3 equiv of *n*-Bu_3SnH, 0.1 equiv of AIBN, PhH (0.05 M), reflux, slow addition 3 h, 60% (3:2 mixture of diastereomers) (reference 40)

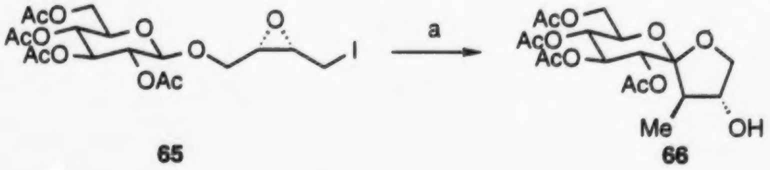
position of the allylic system. Carbon radical **56**, resulting from 1,5-hydrogen abstraction, added to the allylic stannane, regenerating both the double bond present in the precursor, and the radical $R_3Sn\cdot$ which carries on the chain process.

Several variants[41] of this method have also been reported. In these examples, the functional group attacked by the radical source, which also triggered the epoxide radical fragmentation, remained in the final product (Scheme 16).



Scheme 16 *Reagents and conditions:* (a) 0.3 equiv of *n*-Bu_3SnH, AIBN, PhH, reflux 67% (reference 41a); (b) 0.3 equiv of *n*-Bu_3SnH, AIBN, PhH, reflux 80% (reference 41b); (c) 0.15 equiv of $(PhS)_2$, 0.1 equiv AIBN, *hv*, PhH, reflux, 82% (reference 41c); (d) cat. $(n\text{-}Bu_3Sn)_2$, PhH, *hv*, 75% (reference 41d)

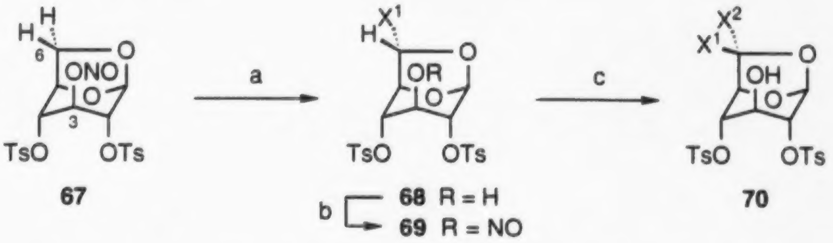
Ferrier[42] used this strategy for the construction of spiro glucosides (Scheme 17). In this example, the rearranged allyl alkoxy radical abstracted the anomeric hydrogen (1,5-hydrogen transfer) and the resulting radical then cyclized onto the terminal double bond of



Scheme 17 *Reagents and conditions:* (a) *n*-Bu_3SnH, AIBN, PhH, *hv*, addition 8 h, 12 h, 68% (reference 42)

the aglycone, to give mainly spiro compound **66**. Interestingly, the other epimer of epoxide **65** led to the formation of a mixture of products. Another example of a similar rearrangement was observed by Murphy et al.[43]

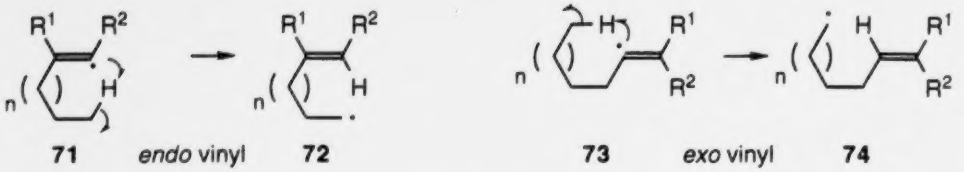
Lopez, Alonzo and Fraser-Reid[44] used a convenient modification of the Barton reaction to form a carbon-carbon bond at an unactivated position in rigid carbohydrates (Scheme 18). The alkoxy radical was generated by treatment of nitrite **67** with tin hydride, and then the 6-*endo* hydrogen of the carbohydrate was abstracted. The translocated radical reacted with the radicalophile X^1 (acrylonitrile), which approached stereoselectively from the *exo* face of the 1,6-anhydroglucopyranoside. This sequence was repeated (**68**→**69**→**70**) with the radical being quenched by a second radicalophile X^2 (tin hydride). This second sequence served to invert the stereochemistry at C6. Consequently, both *exo*-**68** and *endo*- **70** isomers can be synthesized in a controlled fashion.



Scheme 18 *Reagents and conditions:* (a) *n*-Bu_3SnH, CH_2=CHCN, 78% (X^1 = CH_2CH_2CN); (b) nitration; (c) *n*-Bu_3SnH, 67% (X^1 = CH_2CH_2CN, X^2 = H) (reference 44)

Intramolecular Hydrogen Abstraction by Vinyl Radicals

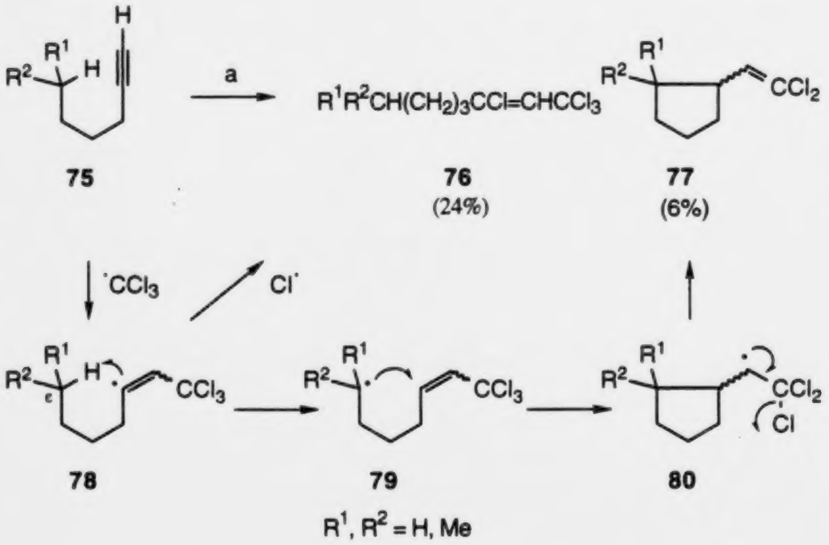
The first carbon radical considered in our survey is the vinyl radical. This reactive radical possesses a unique feature in that the intramolecular hydrogen abstraction can follow two distinct pathways (Scheme 19). In the first mode **71**→**72** (*endo* vinyl), both carbon atoms forming the double bond are involved in the cyclic transition state, unlike the



Scheme 19

second mode **73**→**74** (*exo* vinyl) in which only one carbon of the vinyl system participates. These two possibilities have an important influence on the outcome of the radical transfer.

In 1967, Heiba and Dessau[45] were the first to report the rearrangement of vinyl radicals (Scheme 20). During the free-radical addition of carbon tetrachloride (CCl_4) to acetylene (Kharash reaction), the carbocyclic compounds **77** were isolated in addition to the expected linear product **76**. During this reaction, the $^{\bullet}CCl_3$ radical added to the terminal position of the acetylene, leading to formation of reactive vinyl radical **78**, which

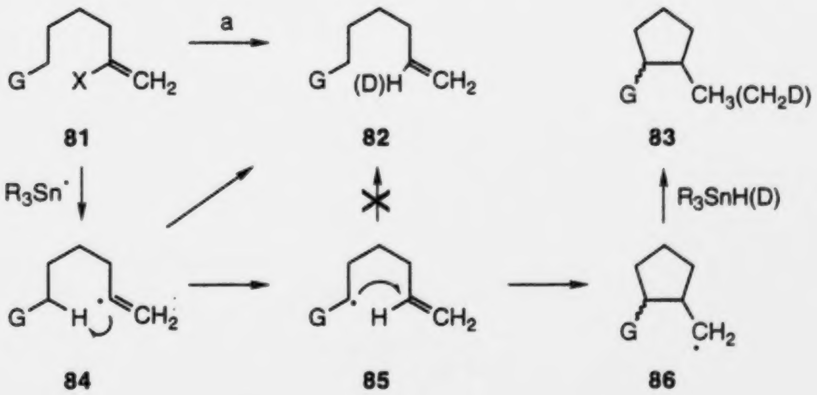


Scheme 20 *Reagents and conditions:* (a) 0.3 M CCl_4, $(PhCO)_2O_2$, 24 h, reflux ($R^1 = R^2 = Me$) (reference 45)

either reacted with the chlorine atom source to give linear product **76**, or captured an ε hydrogen from the carbon chain, to give the intermediate **79**. Addition of the translocated radical to the remaining double bond in a 5-*exo-trig* fashion (**79**→**80**), followed by radical elimination of the halogen, produced cyclic product **77**.

Electron spin resonance measurements have identified the intermediates formed in 1,4-,[46] 1,5-,[46,47], and 1,6[47c]-radical transfers in *endo* vinyl examples, but to our knowledge, no equivalent study on models of the *exo* vinyl type is available.

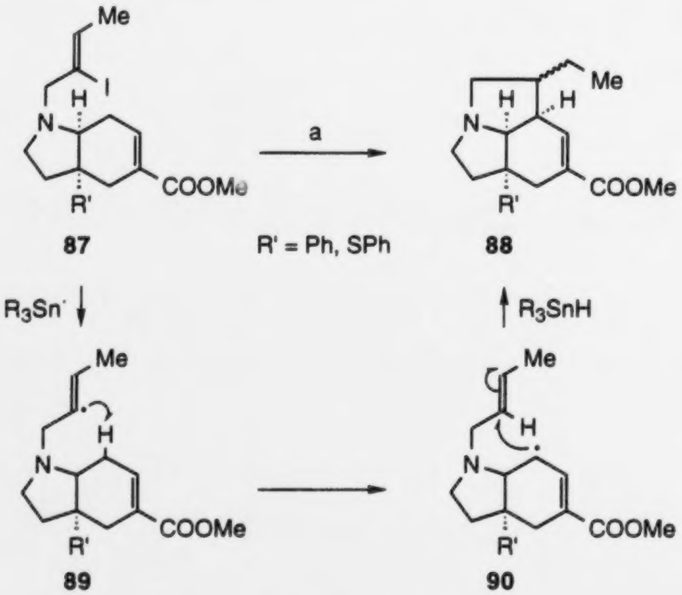
Curran et al.[48] recognized the synthetic value of this free radical rearrangement in the construction of carbocyclic compounds. The influence of radical stabilizing groups (G), attached to the carbon which provided the hydrogen atom during the intramolecular transfer, was investigated (Scheme 21). The vinyl radical was generated by treatment of



Scheme 21 *Reagents and conditions:* (a) cat. n-Bu$_3$SnCl, AIBN, NaCNBH$_3$, t-BuOH, reflux (reference 48a)

vinyl halide **81** (X = I, Br) with trialkyltin radicals. In one experiment, vinyl bromide **81** (X = Br, G = t-BuMe$_2$SiO) was reduced using a deuterated reagent. Since no deuterium was found at the position of hydrogen abstraction, the possible formation of the reduced compound **82** via the translocated radical (**81**→**84**→**85**→**82**) was ruled out. An inverse correlation between C–H bond dissociation energy and yield of cyclization was also observed: the weaker the C–H bond, the better the yield of cyclization.

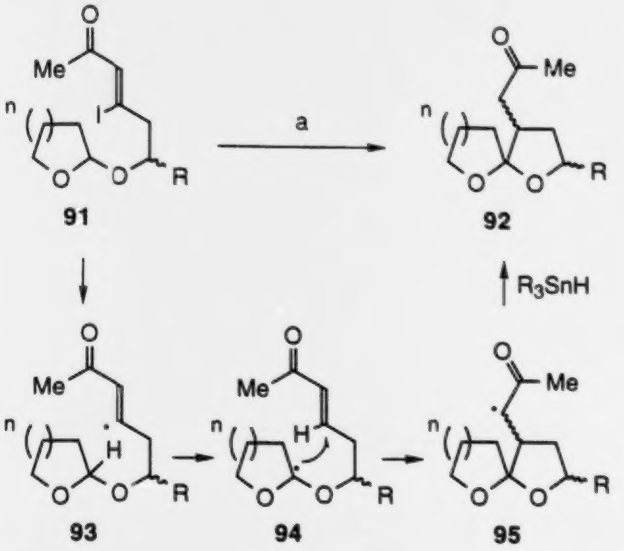
At the same time, Parsons et al.[49] used intramolecular hydrogen abstraction of activated allylic C–H bonds in the synthesis of tricyclic alkaloids (Scheme 22).



Scheme 22 *Reagents and conditions:* (a) *n*-Bu_3SnH, *hv*, PhH (0.01 M), 60–85% (R' = Ph) (reference 49)

In this example, the 1,5-hydrogen transfer (**89→90**) was favored over the possible 6-*exo-trig* radical cyclization onto the conjugated olefin (arrow not shown). This methodology was applied to the construction of five membered rings,[50] bicyclo[3.4.0]nonanes and spiro[4.5]decanes,[51] but failed in the construction of bicyclo[3.3.0]octanes (for which the alternative radical cyclization was faster, to produce bicyclo[3.2.1]octanes).

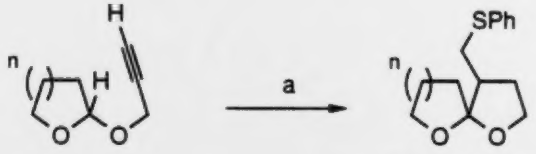
A similar strategy was used by Brown and Simpkins[52] for making spiro acetals (Scheme 23). The vinyl radical, itself generated by the stannane method, abstracted the acetal hydrogen leading to formation of radical **94**. Subsequent conjugated addition to the enone gave spiroacetals **92** as a mixture of isomers. Unfortunately, this radical



Scheme 23 *Reagents and conditions:* (a) 1.2 equiv of *n*-Bu_3SnH, 0.2 equiv of AIBN, PhH, reflux, syringe pump addition, 70% (R = Et, n = 1) (reference 52)

rearrangement failed in more elaborate substrates (carbohydrates).

Griffiths and Murphy[53] built models which imitate the intermolecular hydrogen abstraction that triggers cleavage of DNA strands[54] (Scheme 24). In this reaction, the sulfur radical (PhS•) added to the terminal position of the acetylene, and the resulting vinyl radical rearranged, following a pathway similar to the previous example (Scheme 23). The formation of a multitude of products in these reactions could explain the poor isolated yields of both spiroacetals **97a–b**.

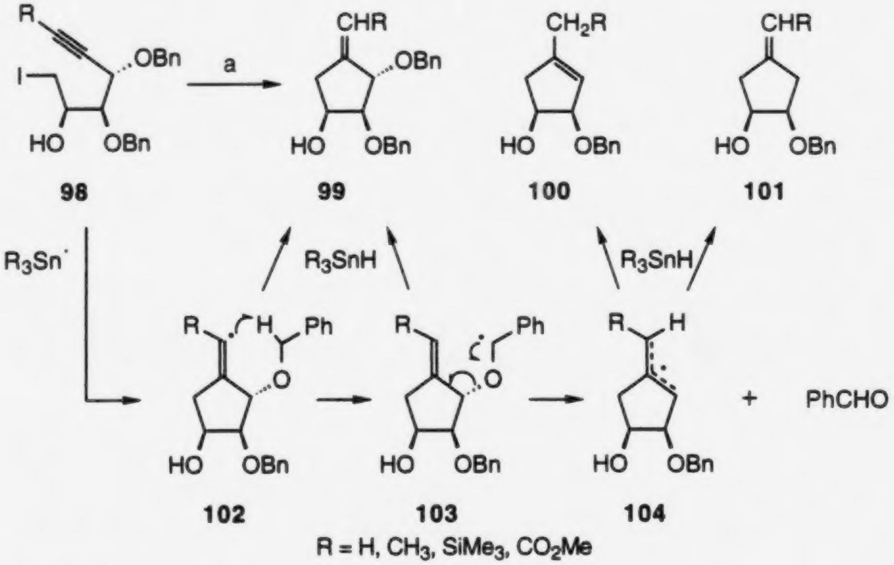


96a n = 1
96b n = 2

97a n = 1 (1.2%)
97b n = 2 (*ca.* 10%)

Scheme 24 *Reagents and conditions:* (a) $(PhS)_2$, *hv*, PhH, slow addition 3 h (reference 53b)

Undesired abstraction of hydrogen by vinyl radicals has been reported,[55] including 1,6-hydrogen transfers observed in model studies of fredericamycin A.[56] For example, Doutheau et al.[55d] observed the lost of a benzyl group during cyclization of halogeno-L-arabinohex-1-ynitol **98** (Scheme 25).



Scheme 25 *Reagents and conditions:* (a) 1.2 equiv of Ph_3SnH, 0.01 equiv of AIBN, PhH, reflux, slow addition 3 h, 80% (**100** + **101**, R = H) (reference 55d)

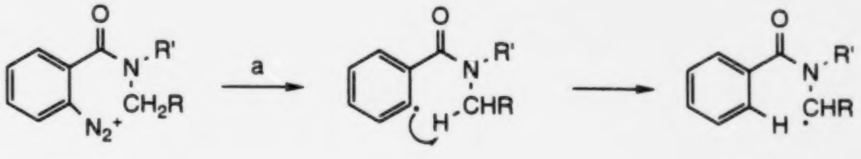
Vinyl radical **102**, formed during radical cyclization of iodide **98**, abstracted a hydrogen atom from the benzyl protective group. The translocated radical **103** fragmented, leading to formation of stabilized allylic radical **104**. Its reduction by tin hydride then gave a mixture of products, **100** and **101**, along with the expected cyclic compound **99**.

Intramolecular Hydrogen Abstraction of Acyl Radicals

Radical abstractions have been reported involving acyl radicals,[57] but to our knowledge, no specific application to organic synthesis has been reported.

Intramolecular Hydrogen Abstraction by Aryl Radicals

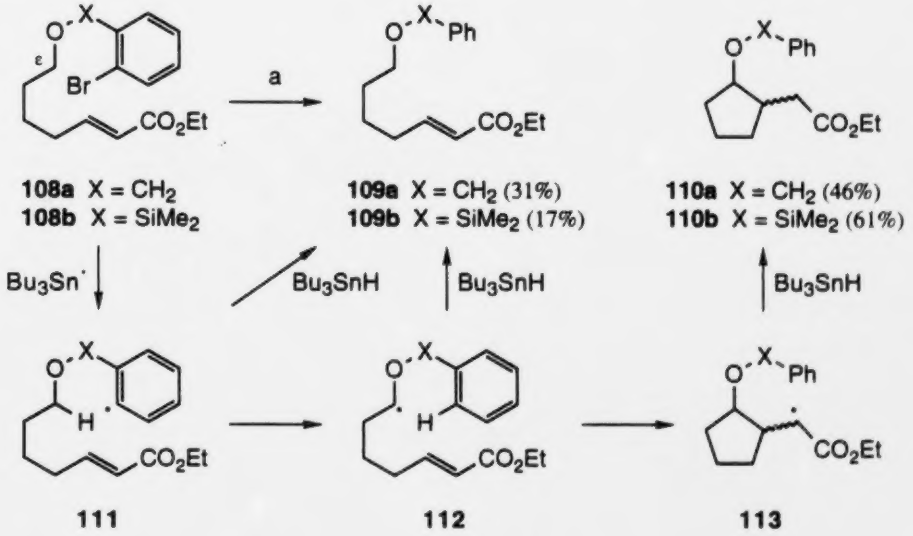
The hydrogen transfer initiated by an aryl radical (Pschorr reaction) was observed as early as 1954 in the decomposition of diazonium ions substituted by *ortho* amide functional groups[58] (Scheme 26). Following this result, pioneering works[59] on similar substrates have established some general principles which still guide even recent developments of this radical rearrangement into useful synthetic tools.



105 **106** **107**

Scheme 26 *Reagents and conditions:* (a) Cu, CuCl, or CuO, additive, H_2O or AcOH, 20 °C (reference 59a)

Curran et al.[48a] recognized the synthetic value of intramolecular hydrogen abstraction by aryl radicals in the formation of 5-membered carbocycles (Scheme 27). In



108a X = CH_2
108b X = $SiMe_2$

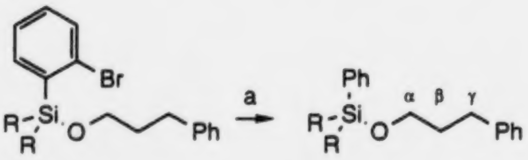
109a X = CH_2 (31%)
109b X = $SiMe_2$ (17%)

110a X = CH_2 (46%)
110b X = $SiMe_2$ (61%)

111 **112** **113**

Scheme 27 *Reagents and conditions:* (a) 0.1 equiv of *n*-Bu_3SnCl, 0.1 equiv of AIBN, 2 equiv of $NaCNBH_3$, *t*-BuOH (0.05 M), reflux, 4–6 h (reference 48a) these examples, the strategy has some resemblance to the construction of a 5-membered ring from a translocated radical obtained by vinyl radical hydrogen abstraction (Scheme 21). The aryl radical, located on a modified protective group and generated by the stannane method from bromide **108**, captured an ε hydrogen. The oxygen-stabilized radical **111** then added to the conjugated olefin to produce the cyclization products **110a–b**, after reduction by stannane.

Having established that the best results were obtained with the silicon-containing protective group, Curran et al.[60] studied the intramolecular abstraction in simple linear and cyclic substrates (Scheme 28). For example, the reduction of linear chain bromides **114a–b** with a deuterated stannane gave reduced products **115a–b**. The distribution of deuterium on the chain showed competition between all possible abstraction processes, but the 1,5-hydrogen transfer was heavily favored. The cyclic substrates showed a higher discrimination for the 1,5-hydrogen abstraction than the linear examples. This method was used in the preparation of rapamycin-d_1 with 61% incorporation of deuterium in the final product.



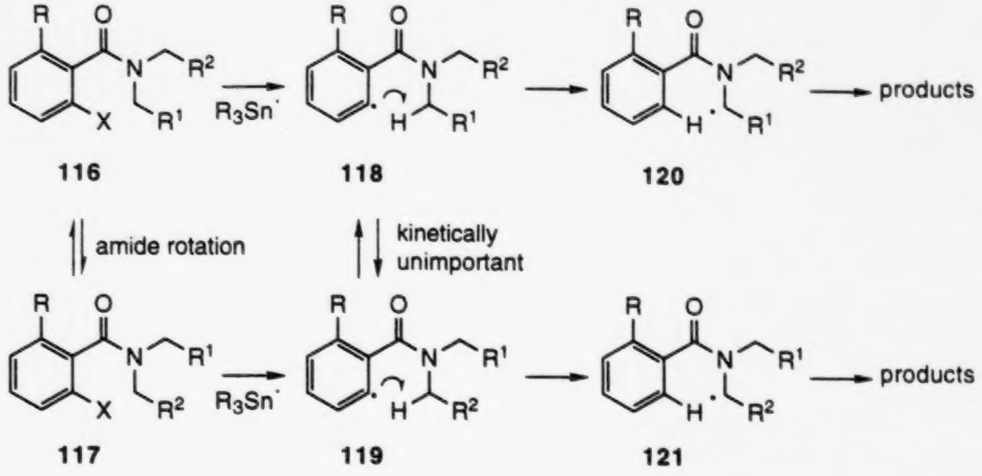
114a R = Me
114b R, R = $(CH_2)_4$

115a R = Me
115b R, R = $(CH_2)_4$

Distribution of D	α	β	γ
115a R = Me	65	11	24
115b R, R = $(CH_2)_4$	74	13	

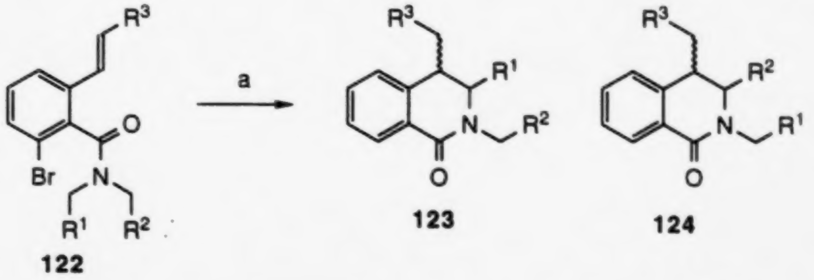
Scheme 28 *Reagents and conditions:* (a) 1.2 equiv of *n*-Bu_3SnD, 0.1 equiv of AIBN, PhH (0.05 M), 80 °C, 4 h (reference 60)

Snieckus,[61] who was inspired by earlier work (see Scheme 26) and by the recent use of translocated radicals to construct 5-membered carbocycles, studied the reactions of α-benzamidoyl radicals (Scheme 29). For these substrates, the rate of rotation around the



Scheme 29 (reference 61)

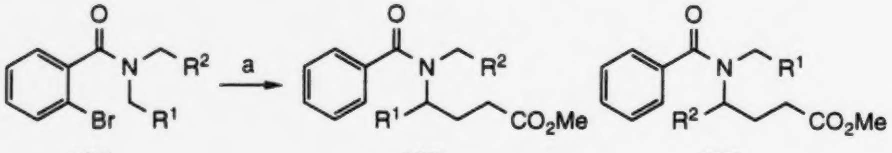
amide C–N bond is much lower than the rate of abstraction.[59b] Consequently, the rotamer distribution of the starting aryl halide (**116**, **117**), evaluated at equilibrium by NMR



Scheme 30 *Reagents and conditions:* (a) 2 equiv of *n*-Bu_3SnH, 5 mol % AIBN, PhH (0.02 M), 80 °C, 67% (R^1, R^2, R^3 = Me) (reference 61)

techniques, largely determined the final product distribution, since interconversion of radicals **118** and **119** does not occur during the lifetime of the aryl radical. These principles were applied to the development of new methodology for the construction of dihydroisoquinolones (Scheme 30). The aryl radical, derived from the corresponding bromide **122**, captured a hydrogen atom α to the nitrogen. Rotation around the amide-aryl C–C bond, followed by radical cyclization, gave products **123** or **124**.

A variation of this method was reported, in which the translocated radical was trapped by electron deficient alkenes, leading to formation of new C–C bonds (Scheme 31). Symmetrical amides ($R^1 = R^2$) generally gave better yields (68–91%) in comparison to unsymmetrical substrates ($R^1 \neq R^2$), which produced two distinct products caused by the lack of chemoselectivity in the radical translocation.

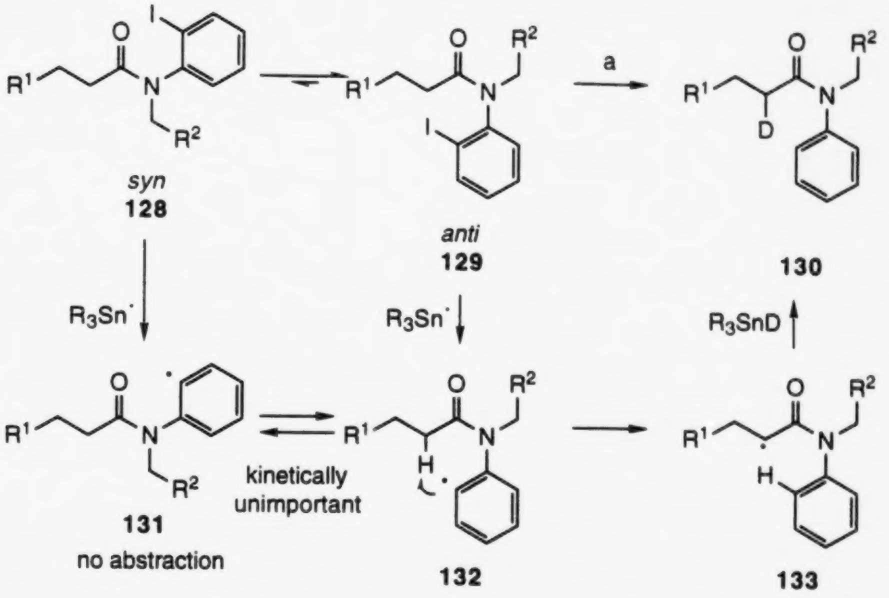


125 **126** **127**

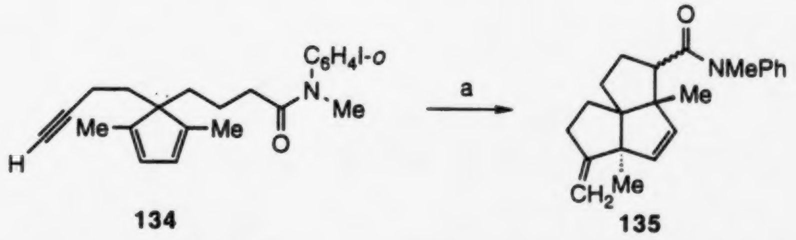
Scheme 31 *Reagents and conditions:* (a) 2 equiv of *n*-Bu_3SnH, 5 mol % AIBN, CH_2=$CHCO_2Me$, PhH (0.02 M), 80 °C (reference 61)

Curran, Abraham and Liu[62,63] reported some intramolecular hydrogen transfers involving amide functional groups. In these examples, the hydrogen atom α to the amide carbonyl was abstracted by the aryl radical (Scheme 32). The ratio of *syn* **128**/*anti* **129** rotamers, determined by ^{1}H NMR techniques, favored largely (5:95) the latter, which is the only one capable of hydrogen abstraction. As in the preceding system of Scheme 29, the radical species **129** conserves its initial geometry, since the amide C–N rotation is slower than homolytic cleavage of the C–I bond and the subsequent radical transfer. Indeed, the intramolecular hydrogen abstraction (**132**→**133**) was very efficient in these substrates, since the content of deuterium α to the carbonyl in the reduced compound was substantial (generally over 80%).

A similar translocated radical was utilized in a series of substrates for radical cyclization. In the example shown, the product of the tandem radical cyclization **135** was obtained in very good yield (Scheme 33).

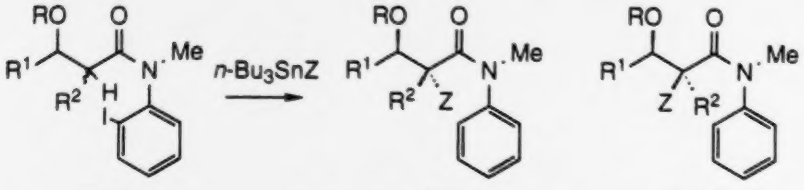


Scheme 32 *Reagents and conditions:* (a) 2 equiv of *n*-Bu_3SnD, AIBN, PhH (0.01 M), 80 °C ($R^1 = R^2 = H$, 89%; $R^1 = n\text{-}C_3H_7$, $R^2 = H$, 91%; $R^1 = H$, $R^2 = CH_2COCH_3$, 84%) (reference 62)



Scheme 33 *Reagents and conditions:* (a) *n*-Bu_3SnH, AIBN, PhH, 80 °C, 75% (mixture 1:1) (reference 62)

Inspired by recent reports of 1,2-asymmetric inductions in radical reactions of acyclic systems, Curran et al.[63,64] used their earlier strategy to generate translocated chiral radicals (Scheme 34). In principle, the reagent (i.e. the radical trap) could exercise some diastereofacial selectivity towards the chiral radical. This new method for the control of stereochemistry in linear chains fell well below initial expectations. Although 1,2-induction



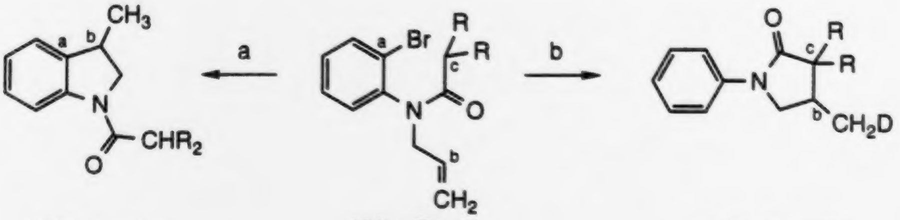
136 **137** **138**

Z = D, $CH_2CH_2{=}CH_2$, $CH_2(CO_2Me)CH{=}CH_2$

Scheme 34

was satisfactory (de = *ca.* 90:10) in the case of reductions (Z = D), the yield of synthetically useful allylations (Z = $CH_2CH{=}CH_2$ or $CH_2(CO_2Me)CH{=}CH_2$) varied from zero to acceptable. In the tertiary series ($R^2 \neq H$) the allylation failed totally.

Jones and Storey[65] predicted the outcome of a radical reaction in which two competitive pathways were possible, either 5-*exo-trig* radical cyclization or 1,5-hydrogen abstraction (Scheme 35). In the first example[66] (**139a**, R = H), the acyl group was allowed to rotate around the aryl-amide C–N bond, and the aryl radical preferentially added to the *N*-allyl protective group (**139a**→**140**). In the second case[65] (**139b**, R = Me), the energy required for this rotation is higher for the dimethylacetyl group. Consequently, the reactive aryl radical captured the remaining acyl hydrogen rather than undergoing the



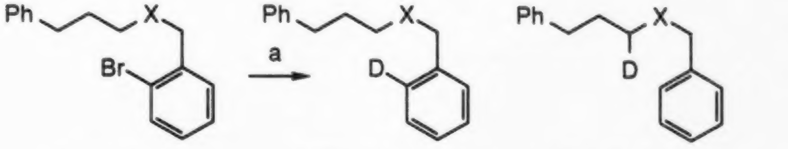
140 R = H

139a R = H
139b R = CH_3

141 R = CH_3

Scheme 35 *Reagents and conditions:* (a) 1.2 equiv of *n*-Bu_3SnH, AIBN, PhH (0.01 M), reflux, slow addition 30 min, 1 h, 91% (R = H) (reference 66); (b) 1 equiv of *n*-Bu_3SnD, $PhCH_3$, reflux, 92% (R = Me) (reference 64) conformational change necessary for radical cyclization. Finally, the translocated radical added to the double bond, and lactam **141** was isolated in excellent yields.

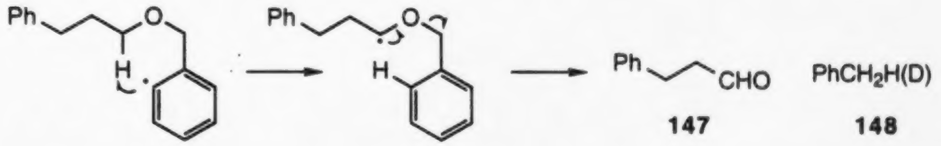
De Mesmaeker et al.[67] investigated the efficiency of intramolecular hydrogen transfer in very simple linear models[68] (Scheme 36). In this study, the side chain heteroatom X was modified , but its position relative to the aryl radical was maintained. Surprisingly, these results showed that the efficiency of the radical rearrangement does not parallel the ability of the heteroatom X to stabilize the radical.[69]



			1,5-hydrogen abstraction total
142a X = O	**143a** X = O (21%)	**144a** X = O (32%)	X = O (79%)
142b X = CH_2	**143b** X = CH_2 (11%)	**144b** X = CH_2 (67%)	X = CH_2 (67%)
142c X = S	**143c** X = S (20%)	**144c** X = S (30%)	X = S (60%)
142d X = NH	**143d** X = NH (55%)	**144d** X = NH (45%)	X = NH (45%)

Scheme 36 *Reagents and conditions:* (a) 1.1 –1.6 equiv of *n*-Bu_3SnD, 0.05–0.10 equiv of AIBN, PhH (0.01 M), reflux (reference 67)

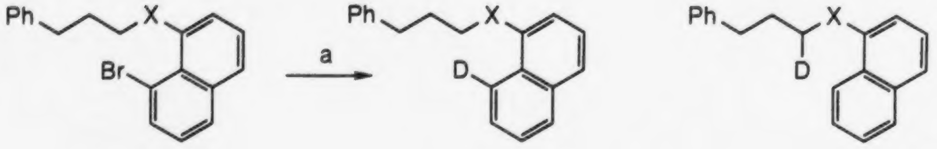
Other rearrangements of the translocated radical which contribute to the overall 1,5-hydrogen abstraction process have also been observed. For example, in the reduction of bromide **142a**, aldehyde[70] **147** was formed by fragmentation of the translocated radical **145** (Scheme 37).



145 **146** **147** **148**

Scheme 37

Two other substrates, derived from naphthalene, in which mobility of the side chain is restricted, were reduced (Scheme 38). The amount of intramolecular radical transfers



149a X = O
149b X = NH

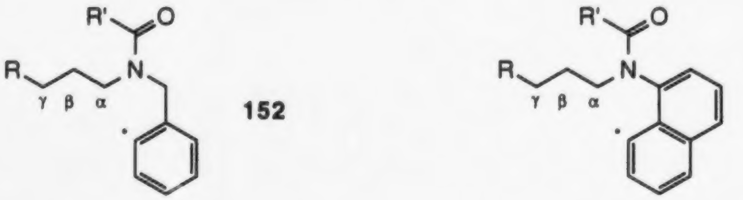
150a X = O (7%)
150b X = N (16%)

151a X = O (93%)
151b X = NH (84%)

Scheme 38 *Reagents and conditions:* (a) *n*-Bu_3SnD, AIBN, PhH (0.01 M), reflux, (reference 67)

were generally higher in these examples, with exclusive selectivity for 1,5-hydrogen abstraction.

De Mesmaeker et al.[71] also studied the behavior of radicals **152** and **153** in the intramolecular hydrogen transfer reaction (Scheme 39). In these models, the aryl radical



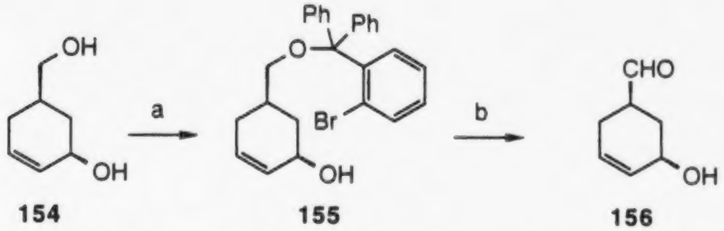
152

153

Scheme 39 *Reagents and conditions:* (a) 1.1 equiv of *n*-Bu_3SnD, 0.05 equiv of AIBN, PhH (0.01 M), reflux (reference 71)

abstracted the hydrogen only from the side chain of the substrates. No deuterium was found in the *N*-acetyl protective group (1,6-hydrogen transfer). In examples of substrate **152** in which a chain substituent weakened the C–H bond (R = Ph, CN), the 1,7-hydrogen transfer became predominant (64–78% of deuterium found at the γ-position).

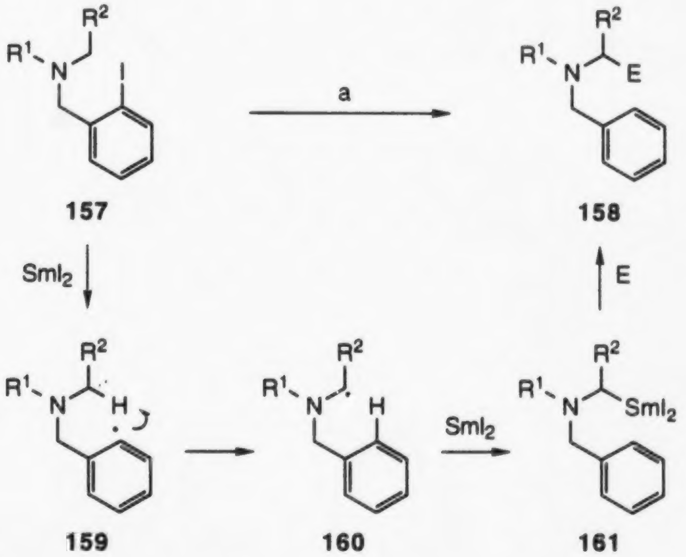
An application of the radical rearrangement-fragmentation (see Scheme 37) was described by Curran and Yu.[72] In this transformation, oxidation of an alcohol occurred under mild *reductive* reaction conditions (Scheme 40). The primary alcohol of diol **154** was selectively protected as its bromine-containing trityl ether **155**. Ether **155** was then treated with tin hydride, using high dilution, to give aldehyde **156** with extrusion of the



Scheme 40 *Reagents and conditions:* (a) DMAP, Et_3N, DMF, 25 °C, 20 h, 52%; (b) *n*-Bu_3SnH, AIBN, PhH (0.001 M), 80 °C, 4 h, 58% (reference 72)

very stable $^{\bullet}CPh_3$ radical. Conventional strategies for this simple conversion involve a battery of protection-deprotection steps.

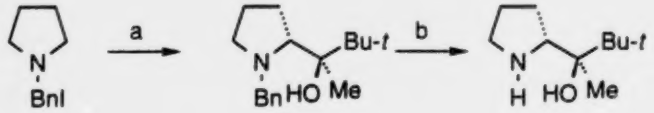
Another method for the formation of C–C bonds α to the nitrogen atom of amines



Scheme 41 *Reagents and conditions:* (a) SmI_2, E (reference 73)

was developed by Ito et al.[73] This procedure is characterized by the use of an electrophile rather than a radical trap in the C–C bond forming reaction (Scheme 41). Samarium(II) iodide initiated homolytic cleavage of the C–I bond, and the resulting radical **159** underwent a 1,5-radical transposition. The carbon radical **160** was then reduced by a one electron transfer from a second samarium(II) iodide, to form organosamarium **161**, which added to the electrophile present in the reaction medium, usually a carbonyl containing substrate.

This principle was nicely demonstrated in the next example, in which alcohol **163** was isolated as a single isomer, and was further debenzylated (Scheme 42).



162 **163** **164**

Scheme 42 *Reagents and conditions:* (a) 3 equiv of SmI_2, *t*-BuCOMe, THP/HMPA, 87%; (b) H_2, $Pd(OH)_2/C$, EtOAc, 99% (reference 73)

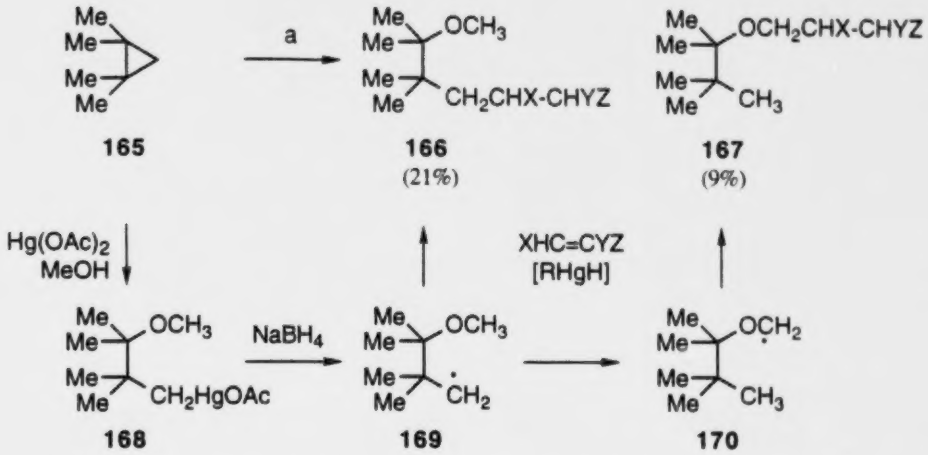
Many other examples of hydrogen transfers, in which aryl radical are responsible for an undesired hydrogen abstraction, have been reported.[59e,74] These examples are not within the scope of this introduction.

Intramolecular Hydrogen Abstraction by Alkyl Radicals.

Of all the various radicals capable of hydrogen transfer, the alkyl radical is the least reactive. Consequently, relatively few useful methods have been developed using the low inherent potential of this radical type to perform an intramolecular abstraction. Therefore, the following section of this introduction will cover examples of intramolecular hydrogen transfer that are at present of little synthetic utility.

Hydrogen abstraction by terminal alkyl radicals in linear carbon chains has been observed in several instances,[75] and during telomerization.[76] As with more reactive radicals, the 1,5-hydrogen shift is largely preferred over other modes of rearrangement.

In one example of a linear chain, Giese et al.[77] reported an intramolecular hydrogen abstraction by a terminal CH_2 radical from a methoxy group (Scheme 43). In this method,

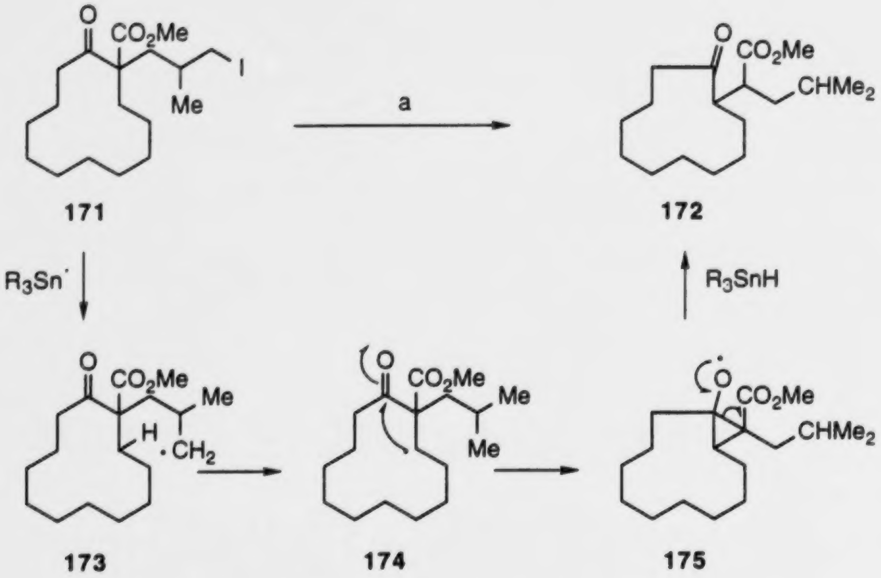


Scheme 43 *Reagents and conditions:* (a) $Hg(OAc)_2$, $MeO_2CCH{=}CHCO_2Me$, $NaBH_4$, MeOH (reference 77a)

the cyclopropane **165** was opened by treatment with a mercuric salt in the presence of methanol. The resulting organomercuric compound **168** was reduced by sodium borohydride, and intermediate **169** was either trapped directly (**169→166**), or underwent a 1,5-hydrogen shift before it added to the electron poor olefin (**169→170→167**). There appears to be no report of an equivalent radical transfer in less substituted cyclopropanes.

Similar rearrangements were also observed in model systems designed to imitate various biological processes.[78] In most examples, homolytic cleavage of carbon-cobalt bonds generated alkyl radicals which were responsible for subsequent hydrogen abstractions.

In a variety of strategies using free radicals to expand cyclic molecules, Baldwin[79], Beckwith,[80] Dowd,[81] (see Scheme 44) and Hart[82] independently reported competitive 1,5-hydrogen abstraction over the planned radical addition to a carbonyl or a cyano group (Scheme 44). Radical **173**, derived from primary iodide **171**, abstracted a hydrogen from the macrocycle, and the resulting radical **174** added to the carbonyl group (**174→175**). The strain of the molecule was then relieved by radical opening of the cyclopropane ring,



Scheme 44 *Reagents and conditions:* (a) *n*-Bu_3SnH, AIBN, PhH, reflux, 31% (reference 81)

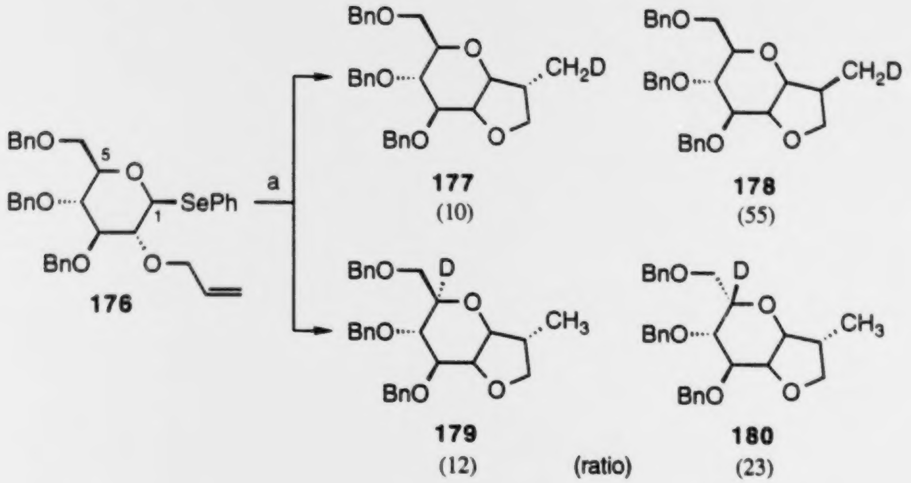
which led to formation of an ester-stabilized radical (not shown), which was finally reduced by the stannane to give the ring contraction product **172**.

Choi and Hart[55a] reported an intramolecular radical shift from a primary radical to a tertiary center adjacent to both a cyclic olefin and a nitrogen atom. Also, Hart and McKinney[83] observed a hydrogen abstraction from an acetal hydrogen by a secondary cyclic radical.

As in many cases of radical cyclization, 1,5-hydrogen transfer is a competitive process with 6-*exo* radical closure. Primary[84] and secondary[85] alkyl radicals are no exception.

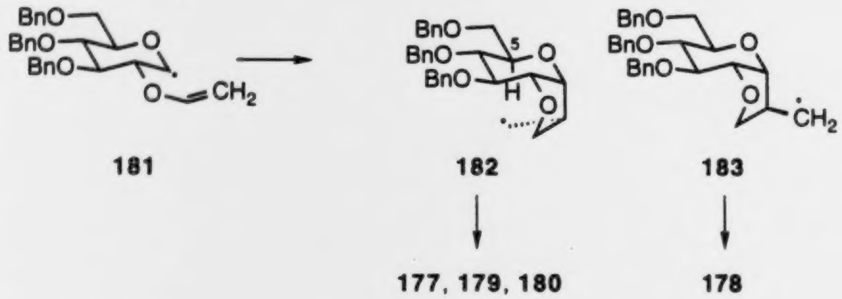
The next examples in this survey share a common feature in that the alkyl radical and the transferred hydrogen are held in close proximity by a rigid (cyclic) structure.

De Mesmaeker[86] reported cases of epimerization at C-5 of glucose derivatives while a radical cyclization took place at the anomeric center (Scheme 45). By the use of a



Scheme 45 *Reagents and conditions:* (a) 1.3 equiv of *n*-Bu_3SnD, 0.1 equiv of AIBN, PhH (0.001 M), reflux, 24 h, combined isolated yields ≥ 90% (reference 86)

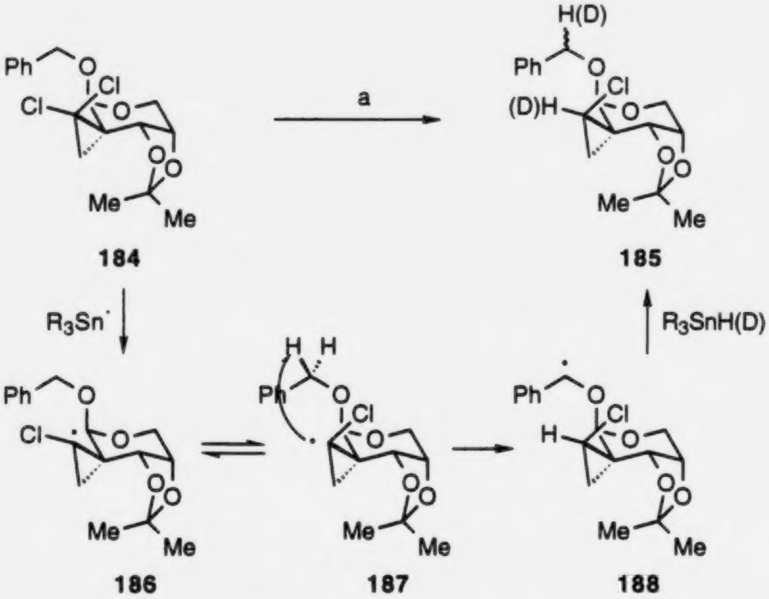
deuterated stannane, the mechanism of the epimerization was determined (Scheme 46). Radical cyclization of anomeric radical **181** produced two primary radicals. The *endo* radical **182** is near the tertiary (C-5) hydrogen, fulfilling the steric requirement for hydrogen transfer. On the other hand, the *exo* radical **183** cannot reach any of the carbohydrate ring hydrogens. Intermediate radical **182** was mainly converted into



Scheme 46

rearranged products (over 75% relative proportion), showing the efficiency of the radical transfer. The same rearrangement was observed with secondary radicals performing the intramolecular hydrogen capture, but the abstraction problem was eliminated in the case of stabilized secondary radicals.[87]

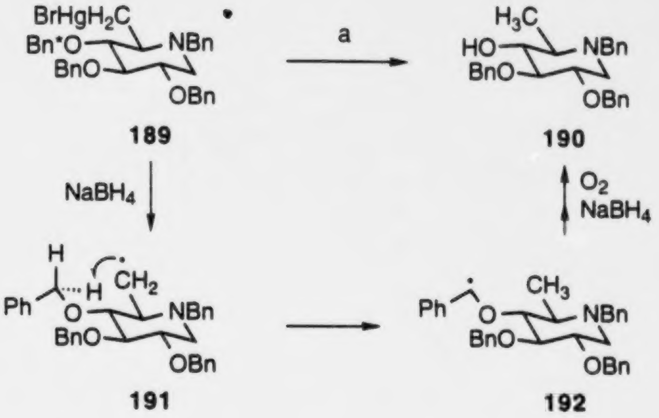
Peters and Powers[88] observed a puzzling selective mono-dechlorination, also in a



Scheme 47 *Reagents and conditions:* (a) 8 equiv *n*-$Bu_3SnH(D)$, AIBN, PhH or PhMe, reflux, 77% (reference 88)

carbohydrate derivative (Scheme 47). Despite the use of a large excess of reducing agent, monochloride **185** was isolated in good yield, as a single isomer. By using a deuterated stannane, it was established that the cyclopropyl radical abstracted hydrogen from the 6-benzyl protective group (**187→188**). This radical rearrangement was therefore responsible for the observed selectivity.

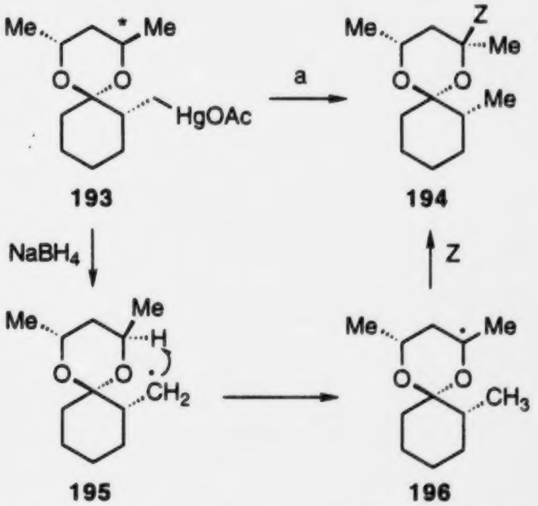
Ganem et al.[89] reported a similar radical transfer from a primary radical to the benzylic position (Scheme 48). The rearrangement (**191→192**) was optimized when both substituents were equatorial (as in the example shown). The benzyl group (see * in **189**) was also cleaved during the reaction: the benzylic radical **192** was oxidized by molecular



Scheme 48 *Reagents and conditions:* (a) $NaBH_4$, O_2 (high flow), DMF, 68% (reference 89)

oxygen, and the oxidation product was reduced to the benzaldehyde hemiacetal, which was finally hydrolyzed during the work up.

Araki et al.[90] also observed 1,6-hydrogen abstraction by a primary radical from a benzylic position in a carbohydrate structure.

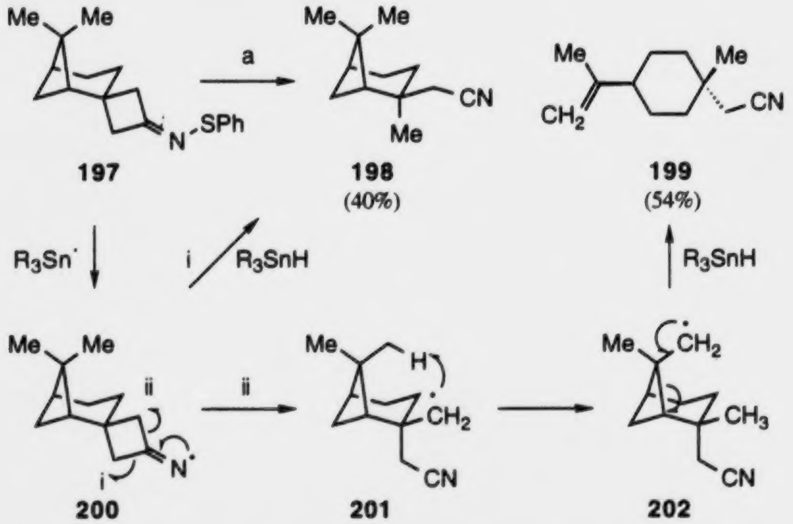


Z = H, CH_2=$CHCO_2Me$, CH_2=CHCN, CH_2=CClCN

Scheme 49 *Reagents and conditions:* (a) $NaBH_4$, CH_2Cl_2, H_2O, (Z = 1 equiv of CH_2=CHCN, 46%) (reference 91)

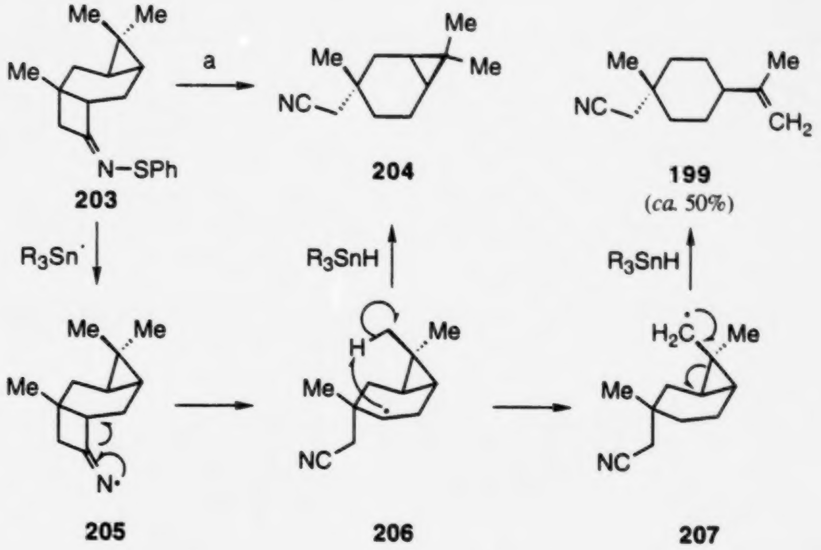
Sugimura et al.[91] mentioned a 1,5-hydrogen transfer in another rigid substrate (Scheme 49). Clean epimerization occurred at the indicated center (*) of optically active acetal **194** during radical reduction of the organomercurial **193** (Z = H). The primary radical **195** underwent a 1,5 hydrogen transfer, and the approach of the incoming reagent (Z) to the translocated radical **196** appeared to be controlled by stereoelectronic effects. This valuable information was used in total syntheses of both (+)-ipomeamarone and (–)-ngaione.[92]

Boivin, Fouquet and Zard[93] have reported regiospecific ring cleavage of cyclopropanes during β-scission of iminyl radicals (Scheme 50). The cyclobutane ring was cleaved in two ways (paths i and ii). The primary radical **201**, produced by cleavage pathway ii, captured a hydrogen from the *endo* methyl substituent of the cyclobutane. The translocated radical **202** then caused stereospecific opening of the cyclobutane ring, and gave product **199**. Cyano compound **198** expected from the other *β* scission (path i) was also isolated.



Scheme 50 *Reagents and conditions:* (a) *n*-Bu_3SnH, AIBN, cyclohexane, reflux, slow addition (*ca.* 5 h) (reference 93)

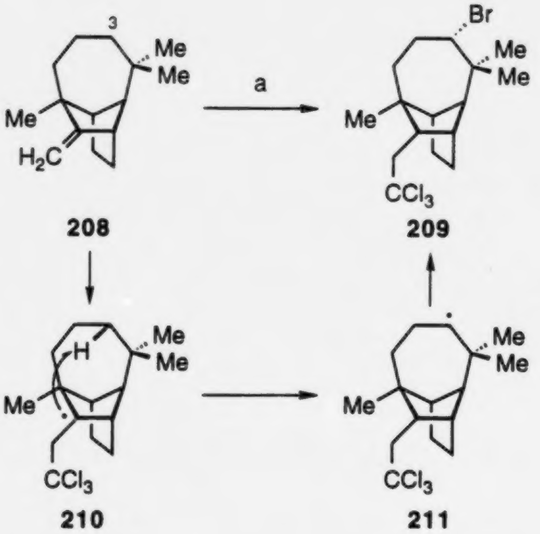
In a second example, the hydrogen of a cyclobutane methyl substituent was abstracted by a secondary radical (Scheme 51).



Scheme 51 *Reagents and conditions:* (a) *n*-Bu_3SnH, AIBN, cyclohexane, reflux, slow addition (ca. 12 h) (reference 93)

Iminyl radical **205** cleaved exclusively in one manner, leading to the formation of ring radical **206**, which was either reduced directly (**206→204**), or underwent an alternative 1,5-radical transfer before the reduction by tin hydride (**206→207→199**).

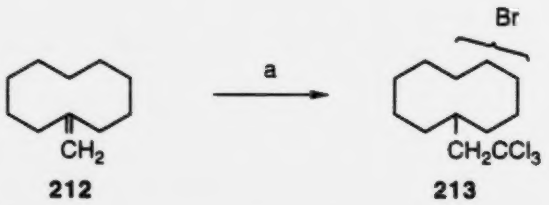
The last set of intramolecular hydrogen transfers to be discussed involve a transannular radical rearrangement. The first example of these hydrogen abstractions by alkyl radicals was reported by Helmlinger and Ourisson[94] in rigid sesquiterpenes (Scheme 52). During the radical addition of trihalogenocarbon to the exocyclic olefin of longifolene **208** (Kharash reaction), the tertiary radical **210** abstracted hydrogen from the (C-3) methylene group. The relief of transannular interactions[95] is probably responsible for the efficiency of this rearrangement whose characteristic feature is that it gives a secondary radical from a tertiary radical. Finally, the translocated radical **211** captured bromine from the least hindered face of the molecule to produce bromide **209** as a single isomer.



Scheme 52 *Reagents and conditions:* (a) $CClBr_3$, *hv*, reflux, 6 h, 76% crude, 30% recrystallized (reference 94)

A similar reaction was used by Jadhav and Nayak[96] in the synthesis of 3β-chlorolongifolene. The radical nature of this transannular hydrogen migration was recently proved by Zard et al.[97]

Fisch and Ourisson[98] reported a rearrangement of radicals in a less rigid 10-membered ring (Scheme 53). In a manner similar to the longifolene example, the tertiary radical, formed after the addition of $^{\cdot}CCX_3$, abstracted hydrogen from one of the transannular methylene groups. Although the 1,5-hydrogen transfer was preferred, analysis of the complex ^1H NMR spectrum could not rule out other potential rearrangement pathways.



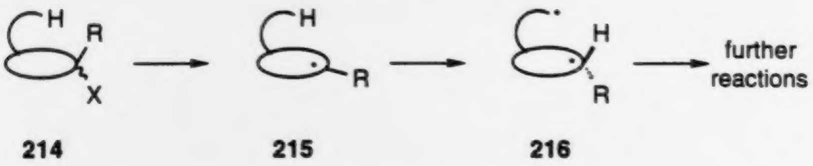
Scheme 53 *Reagents and conditions:* (a) CCl_3Br, *hv*, 37% (reference 98)

An identical intramolecular hydrogen abstraction was observed by Breslow.[99] The initial radical was generated by homolytic cleavage of the substrate-coenzyme B_{12} (carbon-cobalt) bond.

Other examples of transannular hydrogen transfers have been observed in 8-membered rings,[100,78b] in the *trans*-bicyclo[5.3.1]undecane skeleton,[101] and in 11-membered rings.[102]

II DISCUSSION

During the radical spirocyclization of models related to fredericamycin A, some undesired 1,6-hydrogen abstraction was observed (Chapter 1), and our efforts were afterwards directed at finding a means to avoid this side reaction, since it interfered with our synthetic plans. These subsequent researches turned our attention to the possibility of developing synthetically useful processes based on intramolecular hydrogen transfer, and we considered the possibility summarized in Scheme 54.



Scheme 54

Homolytic cleavage of the C–X bond of compound **214**, initiated by a chemical method (use of a stannane reagent for example) would lead to the formation of carbon radical **215**. In principle, this radical could capture a hydrogen atom from a suitably located group, with stereochemical control at the carbon center marked with an asterisk. The translocated radical **216** could be reduced or could undergo further rearrangement. The overall transformation would constitute a potentially useful way of controlling stereochemistry.

For the above reaction to occur, certain requirements would have to be fulfilled, and these were evaluated for each of our proposed models.

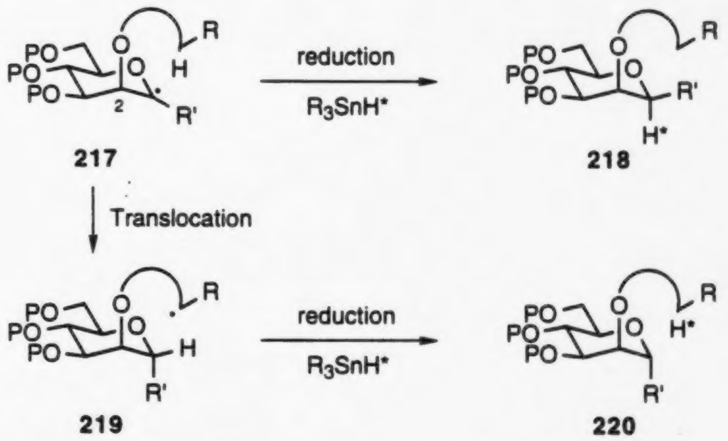
An essential factor is the proximity of the hydrogen to be transferred and the radical triggering the transfer.[4] These distances were evaluated by examination of Dreiding models.

A widely accepted principle suggests that the three atoms participating in the transition state of efficient hydrogen transfers are quasi colinear.[3] This parameter was also evaluated by inspection of Dreiding models.

From thermodynamic considerations, we assumed that the translocated radical had to be more stable than the radical performing the translocation. The relative stability of the initial and translocated radicals was evaluated from tables of C–H dissociation energy.[69,103] In most examples, we relied on weakening effects provided by the presence of substituents adjacent to the hydrogen that was to be abstracted in the translocation.

Mannosyl Radical

The stereospecific construction of C-glycosidic bonds in carbohydrate chemistry is a very active field of research.[104] Our general strategy of stereochemical control by a remote functional group was evaluated with the mannosyl radical (Scheme 55). The mannosyl radical could be reduced by two different routes. It could react directly with the stannane reagent to give compound **218**, having substituent R' in the equatorial conformation. The incoming hydride would necessarily approach from the opposite side to the 2 substituent (1,2-asymmetric induction). Alternatively, a second mode of reduction

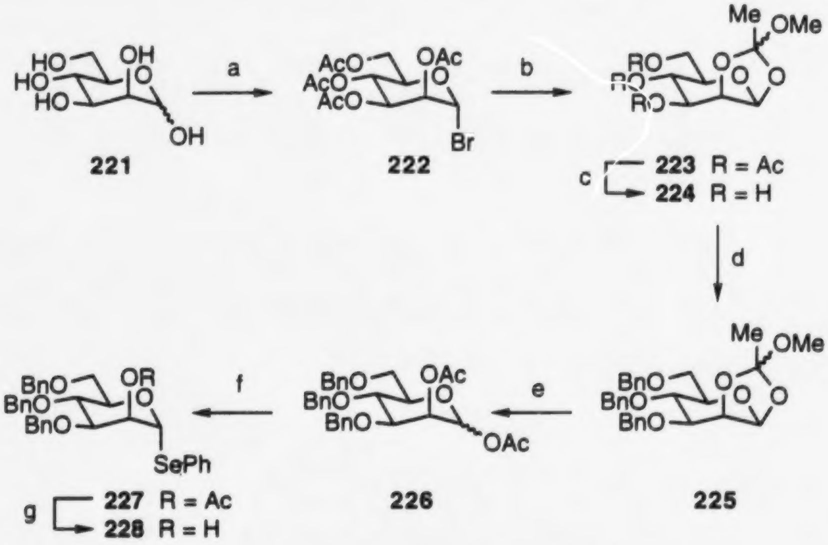


Scheme 55

would involve hydrogen abstraction from a modified OH protective group by the mannosyl radical (**217**→**219**). The resulting radical **219** would finally be reduced to compound **220**, having substituent R' axial.

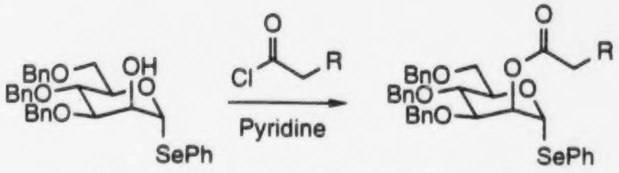
Tri-*O*-benzyl mannosyl selenide[105] was a suitable substrate to test our hypothesis (R' = H). We also chose a modified acetate to protect the free alcohol (C-2), in which the translocated radical would be captodative,[106] as a source of transferrable hydrogen.

Selenide **228** was obtained from D-Mannose **221** following well established procedures[107,105] (Scheme 56).



Scheme 56 *Reagents and conditions*: (a) Ac_2O, $HClO_4$, 30-40 °C, addition 0.5 h, P (red), Br_2, < 20 °C, then H_2O, < 20 °C, rt, 2 h (reference 107a); (b) 2,6-lutidine, MeOH, $CHCl_3$, rt, 24 h, no yield reported (reference 107b); (c) NH_3, MeOH, rt, overnight; (d) NaH, DMF, 15 °C, BnBr, addition 0.5 h, 5 h, 85% (reference 107c); (e) AcOH, H_2O, 100 °C, 4 h, 95% (reference 107d); (f) PhSeH, $BF_3{\cdot}Et_2O$, no yield reported (reference 105); (g) MeONa, MeOH, no yield reported (reference 105)

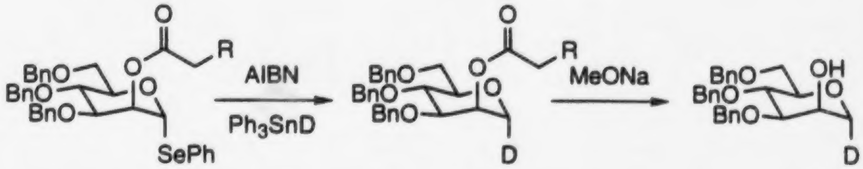
Acetylation (hydroxyl group at C-2) of mannosyl selenide **228** with either methoxyacetyl chloride[108] or phenylacetyl chloride[109a] in the presence of pyridine gave selenides **229** and **230** respectively (Scheme 57).



228 R = OMe, Ph **229** R = OMe (71%)
230 R = Ph (82%)

Scheme 57

Treatment of either selenide **229** or **230** at reflux in benzene with triphenyltin deuteride[110] and AIBN gave the corresponding esters **231** (Scheme 58). Spectroscopic data for both



229 R = OMe
230 R = Ph

231 R = OMe (66%)
232 R = Ph (27%)

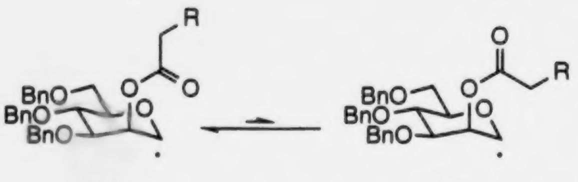
233

Scheme 58

reduced compounds (^{1}H NMR) showed that the mannosyl radical was reduced directly by the stannane. There was no evidence of hydrogen transfer in these two substrates. Moreover, the stannane approached the mannosyl radical with the expected axial trajectory[111] (1,2-asymmetric induction). The presence of deuterium on the carbohydrate ring was also confirmed (mass spectroscopy) from measurements on alcohol **233** obtained by ester hydrolysis of reduced compounds **231**.

Various reasons can be suggested for the failure of this model. The mannosyl radical **217** (Scheme 55), which is stabilized by the presence of the ring oxygen, might not have sufficient reactivity to abstract acetyl hydrogens. Also, the energy demand for the conformational change[112] of the lower energy *E*-conformer **234** to the more congested *Z*-

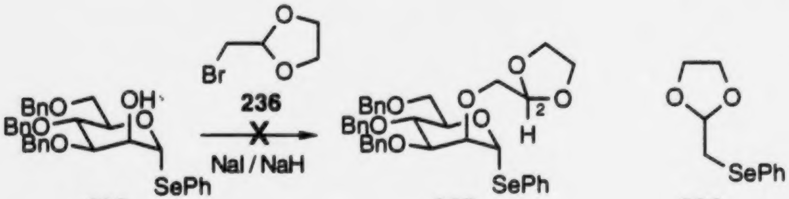
conformer **235** (Scheme 59), might be too large, the latter conformation being a prerequisite for the hydrogen transfer.



Scheme 59

Hydrogen abstraction by alkyl radicals from C-2 of 1,3-dioxolanes has been reported.[83] Based on this precedent, we planned to attach a similar group to our carbohydrate substrate and to test this model again for intramolecular hydrogen transfer **217→219** (Scheme 55).

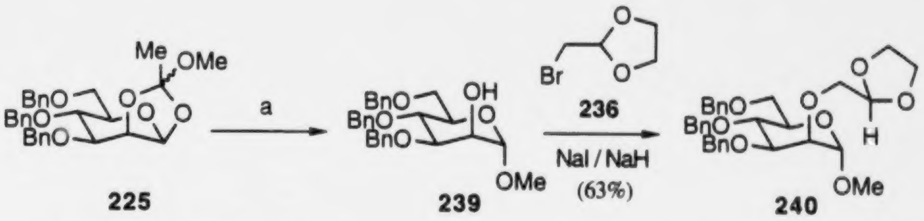
Treatment of a solution of alcohol **228** with 2-bromomethyl-1,3-dioxolane **236**[109a,113] in the presence of sodium hydride and sodium iodide produced none of the desired selenide **237** (Scheme 60). Instead, selenide **238** was isolated (but not fully



Scheme 60

characterized). This result suggested the expulsion of the anomeric selenide from substrate **228**, followed by nucleophilic substitution on halide **236** (either bromide or iodide).

The same conditions were repeated on the less sensitive methyl mannopyranoside **239**,[114] derived from orthoester **225**,[107c] and alkylated compound **240** was obtained in reasonable yield (Scheme 61). This result shows that the conditions we had chosen for protection of the free hydroxyl (C-2) group were appropriate, although they did not work on the desired substrate. Other methods for linkage of the dioxolane group and mannosyl selenide **228** (Scheme 60) were tried, and all failed. Thus, no other derivatives of the



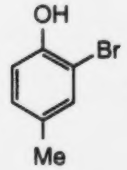
Scheme 61 *Reagents and conditions:* (a) Ac_2O, MeOH, reflux, 18 h (reference 114)

mannosyl series were prepared, and further studies of this model were abandoned.

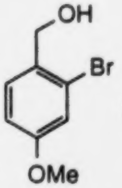
Aryl Radicals

Realizing that the mannosyl radical failed to fulfill our general objectives, we decided to investigate the behavior of aryl radicals. Many examples of intramolecular hydrogen abstraction, in which this reactive carbon radical was involved, have been reported (Introduction, Chapter 2).

In our preliminary investigation, radical precursors would be constructed from two simple templates: 2-bromo-4-methylphenol[109a,115] **241** and 2-bromo-4-methoxybenzylalcohol **242**. This substitution pattern was initially chosen to simplify the evaluation of



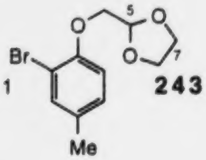
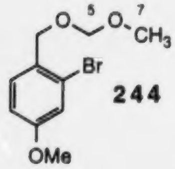
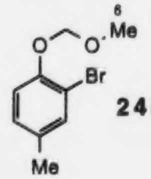
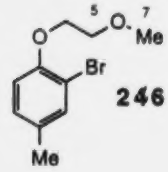
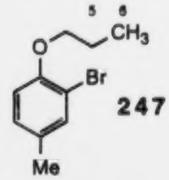
241



242

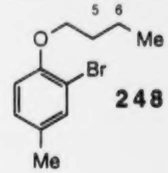
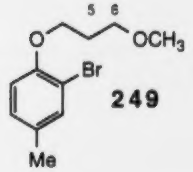
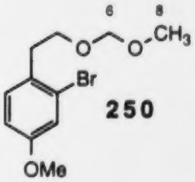
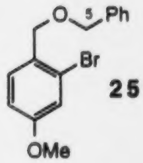
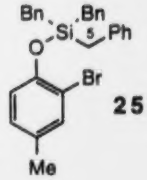
hydrogen transfer efficiency in the reduced products, as simple integration of the proton signals (^1H NMR) in the aromatic region could be used.[116] Later on, we also used ^2H NMR spectroscopy for this assessment.

Table 1: Reduction of Aryl Bromides by Deuteriated Stannane

			Yield[a, b]	Distribution of Deuterium[c]				Method
				Direct	1,5	1,6	1,7	
Entry 1		**243**	(mixture)	0.93	0.06	—	< 0.01	A
			(*ca.* 27%)		*			B
Entry 2		**244**	(82%)	0.97	0.00	—	0.03	A
			(69%)	≈ 0.30	≈ 0.05	—	≈ 0.65	B
Entry 3		**245**	(mixture)	≈ 0.60	—	≈ 0.40	—	A
Entry 4		**246**	(68%)	0.69	0.26	—	0.05	A
Entry 5		**247**	(49%)	0.87	0.13	0.00	—	A

Key: **Method A**: the stannane and the aryl bromide were mixed at the beginning of the reaction; **Method B**: the stannane was added slowly (syringe pump); (a) Yields not optimized; (b) Most reduction products were not fully characterized; (c) In most cases, deuterium distribution was evaluated by ^{2}H NMR spectroscopy. In examples where ^{1}H NMR was used, appropriative ratios are indicated (≈); (*) *p*-Cresol was isolated. See following discussion.

Table 1 (continued)

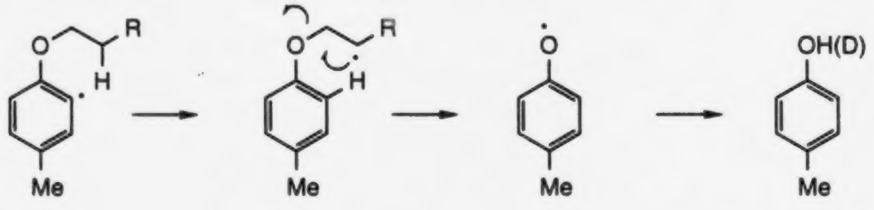
			Yield[a, b]	Distribution of Deuterium[c]				Method
				Direct	1,5	1,6	1,7 / 1,8	
Entry 6		**248**	(*ca*. 50%)	≈ 0.72	≈ 0.13	≈ 0.13	0.00[1,7]	A
Entry 7		**249**	(94%)	0.69	0.00	0.31	—	A
Entry 8		**250**	(mixture)	≈ 0.25	—	≈ 0.25	≈ 0.50[1,8]	A
Entry 9		**251**	(74%)	0.38	0.62	—	—	A
Entry 10		**252**	(36%)	0.04	0.96	—	—	A

Key: **Method A**: the stannane and the aryl bromide were mixed at the beginning of the reaction; (a) Yields not optimized; (b) Most reduction products were not fully characterized; (c) In most cases, deuterium distribution was evaluated by ^{2}H NMR spectroscopy. In examples in which ^{1}H NMR was used, approximate ratios are indicated (≈).

Oxygen containing substituents were selected for stabilization of the translocated radical. The beneficial influence of oxygen substituents on intermolecular hydrogen abstraction rates has been shown on many occasions.[117] Also, ether functional groups are easy to prepare and to handle.

Of the possible radical precursors which could be generated from templates **241** and **242**, the following eight were constructed[118] (Table 1, Entries 1–8), and were subsequently reduced.

From these preliminary results, some general trends were clear: (1) Intramolecular hydrogen transfer was more efficient in the presence of an oxygen atom adjacent to a C–H bond (Entries 4 and 5, Entries 6 and 7). (2) More radical translocation was observed with slow addition of stannane. (3) Surprisingly, acetal C–H bonds were not subject more easily to hydrogen abstraction. To illustrate this point, mainly 1,7-radical transfer was observed in substrate **244** (Entry 2, Method B). (4) Fragmentation of translocated radicals (Scheme 62) was observed in compounds originating from the bromophenol **241**, producing *p*-cresol **256**, with no evidence of deuterium on the aromatic ring.



253 **254** **255** **256**

Scheme 62

(5) Other parameters being equal, the 1,5- and 1,6 hydrogen transfer seemed to occur at comparable rates in these substrates (Entries 4 and 7, Entry 6). (6) No abstraction was observed from terminal (unactivated) methyl groups (Entries 5 and 6).

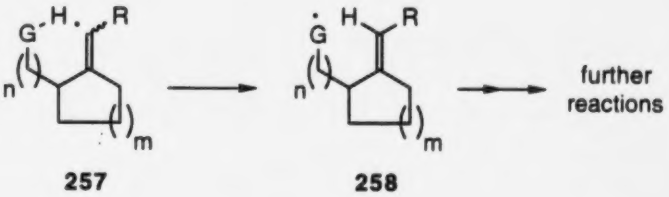
Two additional substrates were prepared in which the so-labelled C-5-hydrogens were benzylic (Entries 9–10). These derivatives displayed the most efficient 1,5-hydrogen transfer. This last example might also benefit from stabilization by the adjacent silicon atom,[119] and from statistical factors (there are now six equivalent benzylic hydrogens compared to two in most other examples).

As anticipated, we observed intramolecular hydrogen abstraction by aryl radicals. However, these results were not promising enough to warrant further development of new synthetic methodology based on this series.

Vinyl Radicals

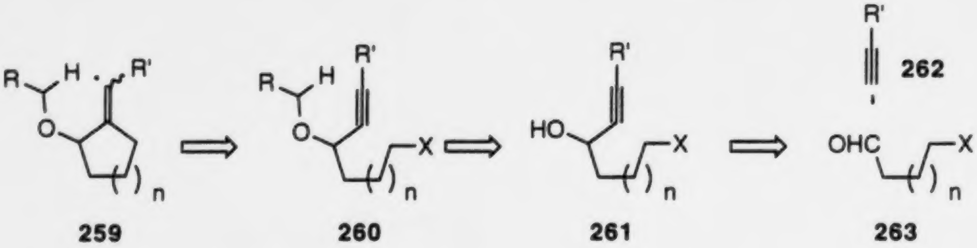
A fair number of synthetically useful methods have been developed from the use of intramolecular hydrogen abstraction by vinyl radicals (see Introduction). All these approaches were characterized by a radical transfer *exo* vinyl radicals (Introduction, Scheme 19), leading to the formation of 5-membered rings.

We imagined a simple strategy for the stereocontrolled synthesis of exocyclic olefins using hydrogen abstraction as a key reaction (Scheme 63). Vinyl radical **257** could capture a hydrogen atom from a properly located group (G). For steric reasons, the intramolecular radical translocation (**257**→**258**) must occur from the same side as the group bearing the transferred hydrogen. Consequently, the stereochemistry of the resulting olefin would be specified. This approach, using a radical rearrangement for stereospecific synthesis of exocyclic alkenes, has not been described elsewhere, but other approaches to such targets have been considered.[120]



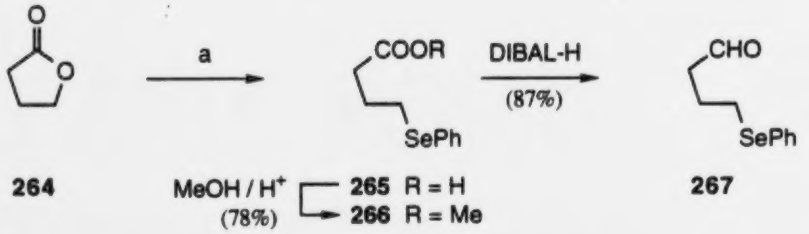
Scheme 63

Prompted by our previous work on fredericamycin A (Chapter 1), we planned to generate the exocyclic vinyl radical **259** by *exo-dig* radical cyclization from a precursor (**260**) equipped with a homolyzable C–X bond (Scheme 64). The hydrogen to be transferred would be situated on a hydroxyl protective group. The propargylic alcohol **261** would be assembled simply by a coupling reaction[121] using a nucleophilic addition of acetylide **262** onto aldehyde **263**.



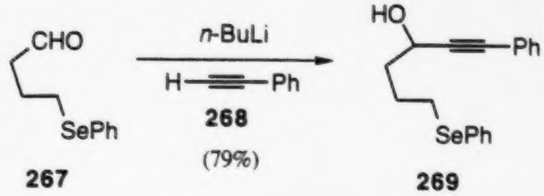
Scheme 64

We first considered the construction of cyclopentane rings (5-*exo-dig* radical cyclization). The homolyzable phenylselenyl group (X = SePh) was chosen for its chemical stability during nucleophilic additions, and the ready accessibility of the corresponding aldehyde **267** (n = 1) from γ-butyrolactone **264** (Scheme 65).



Scheme 65 *Reagents and conditions:* (a) PhSeSePh, NaH, THF, reflux, 45-60 min, rt, HMPA, **264**, reflux, 3 h, 87% (reference 122)

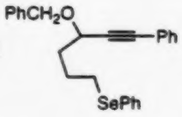
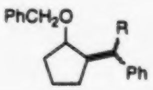
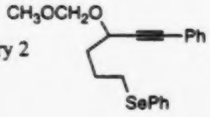
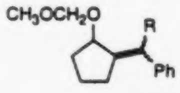
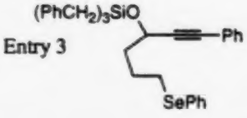
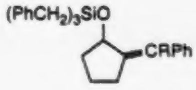
Deprotonation of phenyl acetylene **268** by butyllithium, followed by addition of a solution of aldehyde **267**, gave the coupling compound **269** in good yield (Scheme 66).



Scheme 66

Three compounds in this series were generated from this alcohol (Table 2). Radical cyclization precursors **270** and **273** were designed for an anticipated 1,5-hydrogen abstraction (although a 1,7-radical transfer to the terminal methoxy group is also possible in selenide **273**), and precursor **276** for a 1,6-hydrogen abstraction. The results of the hydroxyl group protections and the subsequent radical cyclizations are summarized in Table 2.

Table 2: Stereochemistry Control of Exocyclic Olefins by Hydrogen Transfer

	Coupling (Yield[a])			Cyclization (Yield[a])		
Entry 1		**270**	79%		**271** R = H **272** R = D	10% 24%
Entry 2		**273**	58%		**274** R = H **275** R = D	90%[b] 91%[b]
Entry 3		**276**	78%		**277** R = D	50%[b, c]

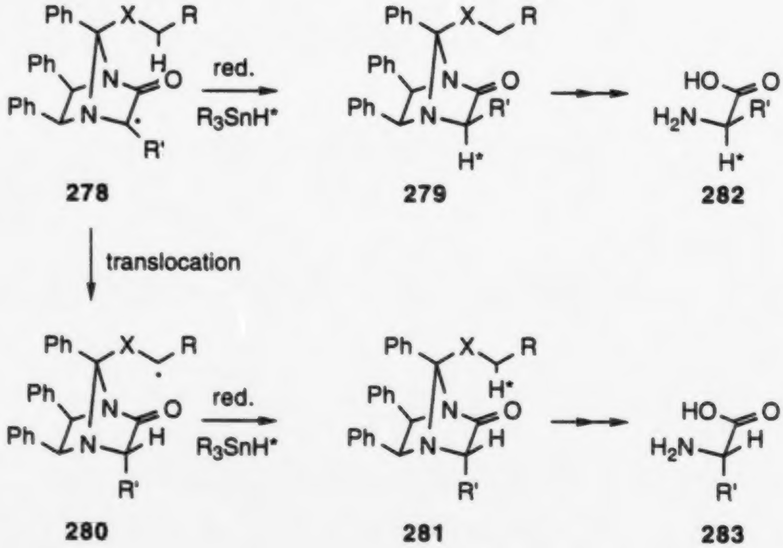
Key: (a) Yields not optimized; (b) Some tin residues (< 10%) contaminated the cyclization product; (c) Only one isomer of unknown geometry was isolated in this experiment.

The low yield in the radical cyclization of substrate **270** was puzzling at first (Entry 1). Also, the data (^{1}H NMR) of the cyclized compound **272** (R = D) showed no sign of 1,5-hydrogen transfer. A previous communication which reported expulsion[55d] of a benzyl group during a similar radical cyclization (Introduction, Scheme 25), furnished a plausible explanation for the behavior now observed. In fact, the presence of benzaldehyde was detected (tlc, silica) in the reaction mixture. Therefore, compound **272** represents only that portion of vinyl radical **259** (R = R' = Ph, n = 1, Scheme 64) which was reduced directly. With no synthetic application foreseen from this radical rearrangement, the identification of other fragmentation products was not undertaken.

Moreover, data from radical cyclization products **275** and **277** did not show any evidence of intramolecular hydrogen transfer under the same conditions. These last results were rather disappointing, especially in the tribenzylsilyl ether case (Entry 3).

Bicyclo[2.2.1]hept-2-yl Radical

Organic chemists have been very active in the synthesis of both natural and unnatural amino acids.[123] Our intent was to use our strategy of Scheme 54 to synthesize α-amino acids in enantiomerically pure form. To achieve this objective, the elaboration of complex substrates preceding the formation of radical **278** was required (Scheme 67), and

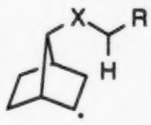


Scheme 67

these compounds would need to be constructed in optically active form. In a manner similar to that of the mannosyl radical (Scheme 55), radical **278** could be reduced directly by the stannane, giving preferentially compound **279**. Alternatively, an internal hydrogen transfer (**278**→**280**) could occur before the reduction, and product **281** would be obtained, which is the enantiomer of compound **279**. Removal of the chiral template (hydrogenolysis of all benzylic C–N bonds), followed by hydrolysis of the resulting amide, would give either enantiomer **282** or its mirror image **283**, provided that high selectivity in the divergent pathways is achieved during the radical reaction.

Norbornyl radical **284** was selected as a simple model, since it retains the essence of the more complicated radical **278** (Scheme 67).

284

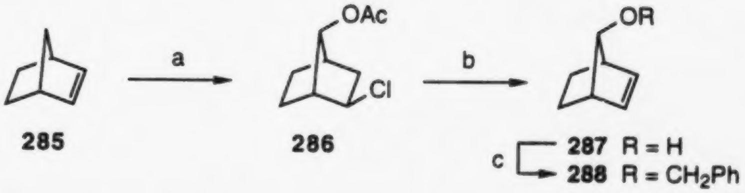


X = O, CH_2, etc…

Also, the carbon geometry of this radical has some pyramidal character,[124] and this deviation from planarity makes this radical slightly more reactive than an unstrained methylene radical.[97]

In our example, the norbornyl radical would be generated by radical deoxygenation,[125] and the transferred hydrogen would be provided once again from a benzyl ether **284** (X = O, R = Ph).[126,127]

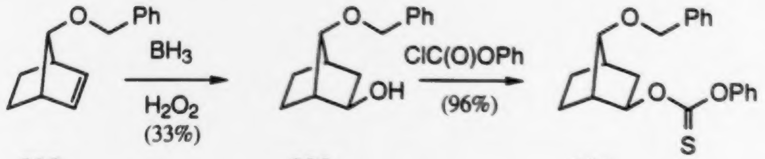
The availability of substrate **288**, derived from norbornylene[128] **285** (Scheme 68),



Scheme 68 *Reagents and conditions:* (a) $CuCl_2$, $PdCl_2$, AcOH, AcONa, 80 °C, 72 h, 84%; (b) *t*-BuOK, DMSO, rt, overnight, then H_2O, 70% crude (reference 128a); (c) NaH, BnBr, THF, rt, overnight, *ca.* 55% (reference 128b)

solved the problem of having both the radical and the activated hydrogen on the same side of the bicyclo[2.2.1]heptane (*syn*).

A hydroxyl group, which would eventually serve as a radical source, was introduced at this stage. Benzyl ether **288** was treated with borane-tetrahydrofuran complex,[129] followed by the usual oxidative work up of the borane ester, to give alcohol **289**[130] (Scheme 69).

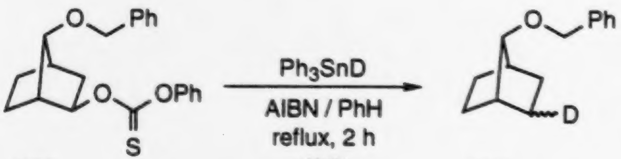


288 **289** **290**

Scheme 69

The free hydroxyl group was converted into thiocarbonyl ester **290** by treatment with phenyl chlorothionoformate.[131,109a]

Treatment of a refluxing solution of radical precursor **290** with triphenyltin deuteride[110] in the presence of AIBN gave compound **291** (Scheme 70), whose spectroscopic properties (^{1}H NMR and ^{2}H NMR) indicated, once again, the absence of intramolecular hydrogen transfer.

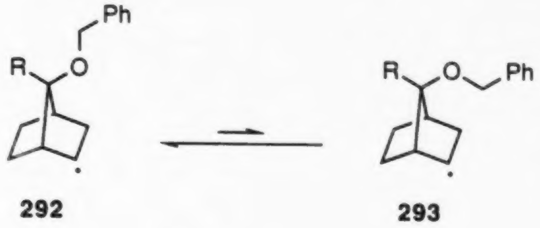


290 **291**

Scheme 70

Also, the data showed that the radical was reduced from both *endo* and *exo* faces (ratio 4:1).

Several explanations can be put forward to account for this result. The relatively low reactivity of the alkyl radical could be largely responsible for the failure of the radical transfer. Also, the fact that the reduction occurred mainly from the *exo* face of the radical suggests that the reagent penetrated easily into the space between the norbornyl radical and bridge substituent. Therefore, the side chain bearing the transferable hydrogen must have been mainly pointing away from the alkyl radical (Structure **292**, R = H) rather than having the necessary conformation for the desired transfer (Structure **293**, R = H, Scheme 71). Of course, if the intramolecular transfer rate had been high enough, the relative amounts of **292** and **293** are of no consequence under Curtin-Hammett conditions.



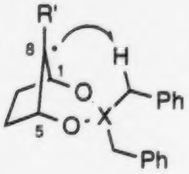
Scheme 71

If this second factor was critical in the failure of the 1,5 hydrogen abstraction, the introduction of a bulky substituent at the 7-*anti* position (R ≠ H) might be helpful, but such models were not constructed.

Fulvene and 1,6-Anhydroglucopyranoside Models

An important piece of information extracted from the study of the mannosyl and norbornylene models was that the design of future models in which an alkyl radical would be involved had to be improved significantly. One suggestion would be to reduce the flexibility of the side chain containing the abstractable hydrogens, so that the substrate conformation would already have some similarity with the required transition state for the intramolecular radical transfer.

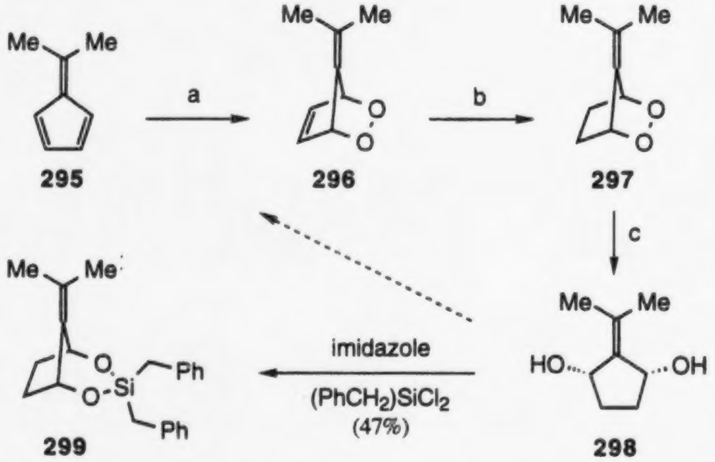
With no synthetic application foreseen, model **294** was designed, in which the 1,3-*cis* diol would be protected as a cyclic ether, and the radical would be generated at the bridge (C-8) position.



294

From examination of a Dreiding model of radical **294**, the steric requirements for the intramolecular hydrogen transfer (i.e. the required proximity of the carbon radical to the benzylic hydrogen), seemed to be fulfilled. Silicon cyclic ether **294** (X = Si) was selected as a first model in this series. The 1,3-*cis* diol portion of this bicyclic compound could be constructed from fulvene.

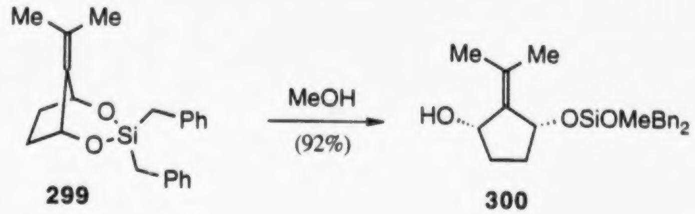
7,7-Dimethylfulvene **295** was converted to diol **298** by a known sequence[132] (Scheme 72). Diol **298** was then treated with dibenzydichlorosilane[134] and imidazole to give bicyclic compound **299**.[135]



Scheme 72 *Reagents and conditions:* (a) *hv*, O_2, tetraphenylporphyrin,[133] CH_2Cl_2, -78 °C, *ca.* 3 h; (b) $KO_2CN{=}NCO_2K$, AcOH, addition -78 °C, 0 °C, 2 h, 63% (over two steps); (c) $NH_2C(S)NH_2$, MeOH, 0 °C, 84 % (reference 132a)

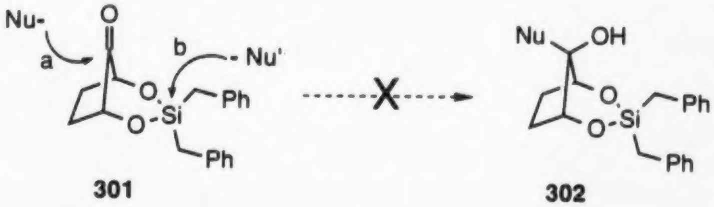
Unfortunately, all attempts to cleave the double bond (ozonolysis) failed to provide any olefin cleavage products. This transformation, which would be anticipated to be straightforward, revealed some of the unusual features of this novel bicyclic compound.

Also, the silicon protective group was very sensitive to nucleophiles. For example, simple stirring of compound **299** as a solution in methanol gave the opened alcohol **300** (Scheme 73). This reaction was accelerated by additives that make the medium basic (K_2CO_3, $NaBH_4$).



Scheme 73

This undesired attack of nucleophiles on the silicon group[136] (Scheme 74, arrow b) became a serious limitation in this approach for the construction of radical precursor **294**.

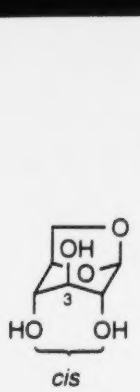


Scheme 74

Our original plan relied on nucleophilic addition (Nu = reducing agents, Grignard reagents) to ketone **301** (Scheme 74, arrow a) leading to the formation of an alcohol **302**, which would then be deoxygenated to generate the desired radical **294**.

Also, the construction of the carbon acetal **294** ($X \equiv C$) by conventional methods would probably fail because of its sensitivity to acid and, in the event, acid catalyzed dehydration of diol **298** produced fulvene **295**[132a] (Scheme 72, dotted arrow). This route was therefore abandoned.

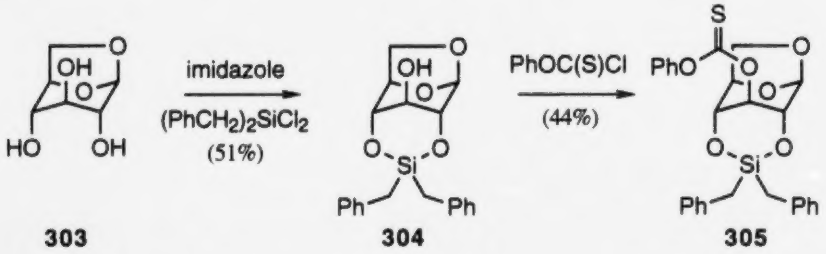
The preference for the $^1C_4$ (D) conformation of 1,6-anhydroglucopyranoside **303** (as shown) in solution[137] was a feature we exploited in the construction of our next model.



303

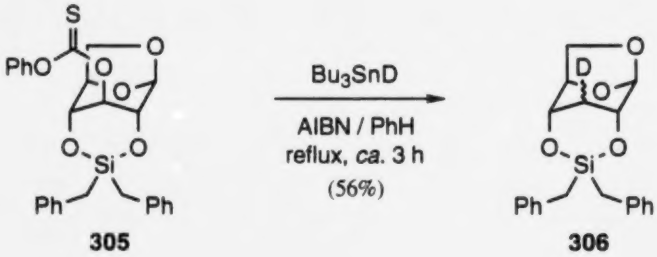
This carbohydrate possesses a 1,3-*cis* diol (positions C-2 and C-4) which could be readily protected, leaving a free hydroxyl group (C-3) which could be deoxygenated by radical methodology. Moreover, addition of strong nucleophiles after the formation of the cyclic silicon ether, would be avoided in this model.

Glucopyranoside **303**[138,109b] was protected as cyclic silicon ether **304**,[139] which was then converted[125] into the desired thiocarbonyl ester **305** in acceptable yields (Scheme 75).



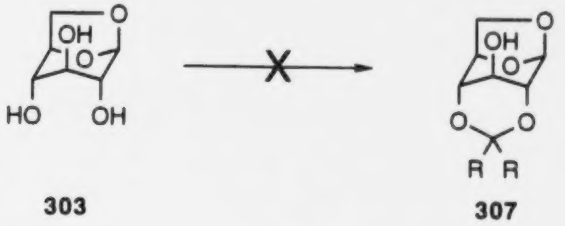
Scheme 75

Treatment of a refluxing solution of thiocarbonyl ester **305** with tributyltin deuteride[109a] in the presence of AIBN gave reduction product **306** with no evidence (^2H NMR) of hydrogen transfer (Scheme 76). The longer Si–O and Si–C bond lengths



Scheme 76

(1.610 Å and 1.872 Å, respectively) might be responsible for these results, therefore placing the radical and the benzylic hydrogen at too large a distance for the hydrogen transfer. In order to verify this hypothesis, the synthesis of carbon derivative **307** (R = CH_2Ph) was envisaged (Scheme 77). Unfortunately, all attempts to make such a compound failed,



Scheme 77

despite the synthesis of the dimethyl equivalent **307** (R = CH_3) reported in a journal we were unable to examine.[140]

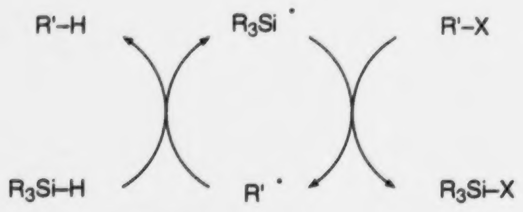
The Turning Point

A substantial reorientation of this project was necessary in order to reach our useful objective: the invention of a new synthetic tool using intramolecular hydrogen abstraction as a key step. In all our previous examples, the source of the transferred hydrogen was always attached to a carbon atom. A departure from this trend would be *the use of better radical hydride donors.*

The Silicon Approach

Organosilanes, such as tris(trimethylsilyl)silane[141] and tris(alkylthio)silanes[142] were recently used in reduction of halides and selenides. Like stannanes or germanes,[2b] these reagents are capable of carrying free radical chains (Scheme 78).

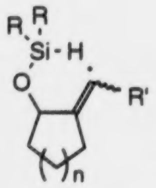
This property of silane reagents containing a Si–H bond could be useful in an intramolecular situation. In principle, the silicon group hydrogen atom could be abstracted by a radical located in the same molecule. Also, the reducing silane could be envisioned as



Scheme 78

a hydroxyl protective group, since several convenient methods[143] for the introduction and the cleavage of silyl ethers are already available.

Initially, the study of the vinyl radical **308** was undertaken. As a result of the intramolecular hydrogen abstraction from the Si–H group by the vinyl radical, control of the stereochemistry at the exocyclic olefin would be achieved (compare with Scheme 63).



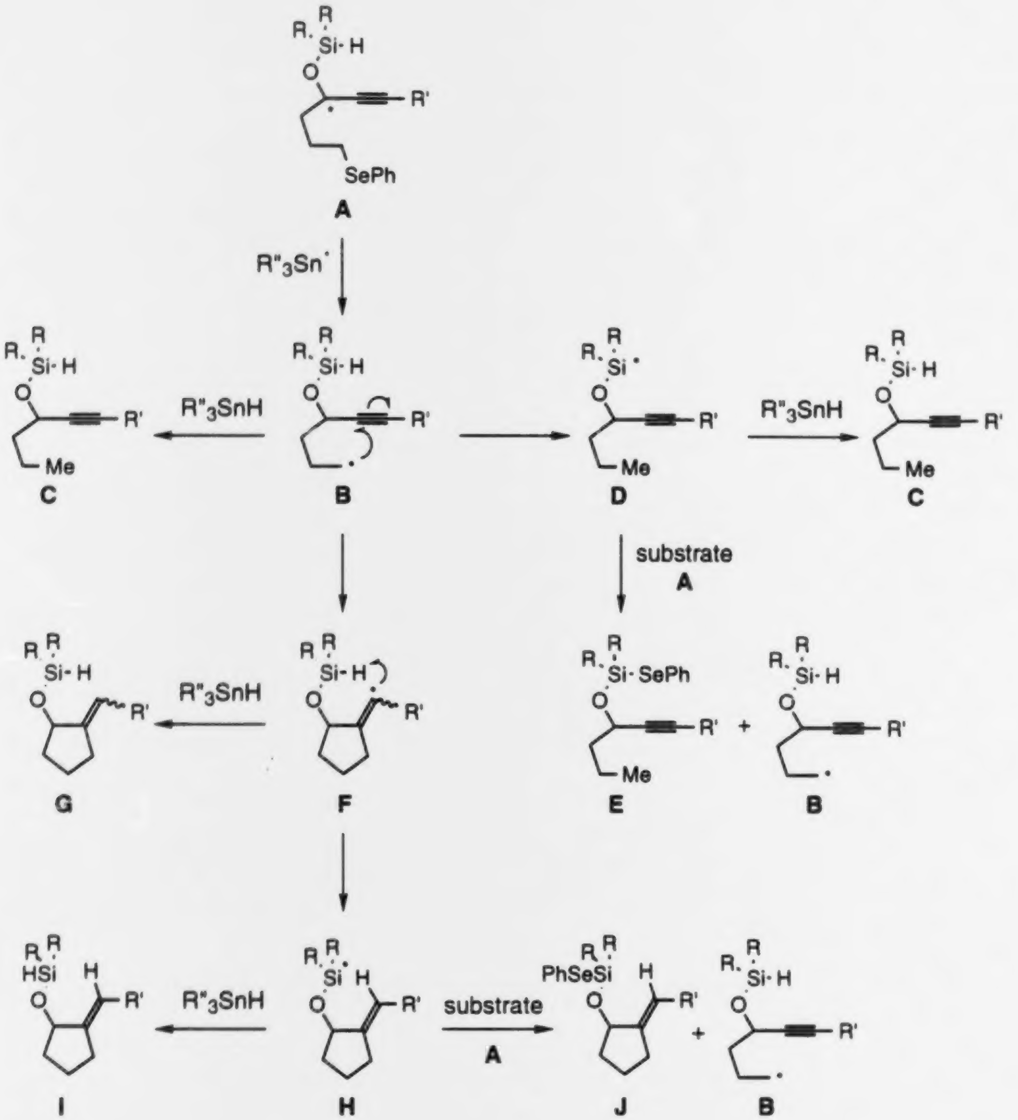
308

In this model, the donor Si-H bond and the reactive radical are five atoms away from each other, a situation in which abstraction was observed previously (Table 2, and Introduction, Scheme 25).

To the best of our knowledge, substrates containing both a radical source and a silicon hydride in the same molecule are unprecedented. Again, the exocyclic vinyl radical **308** would come from a *exo-dig* radical cyclization (see Scheme 64).

Before we conducted any experiments, we evaluated the various pathways a radical reaction performed on substrate A could follow (Scheme 79). We were planning on the use of an external stannane reagent to carry the radical chain process.

Reduced compound **C** could be formed via two possible routes, either the usual reaction of radical **B** with the tin hydride (**A**→**B**→**C**), or by an intramolecular hydrogen capture (**B**→**D**) followed by hydride exchange between the silicon radical and the tin



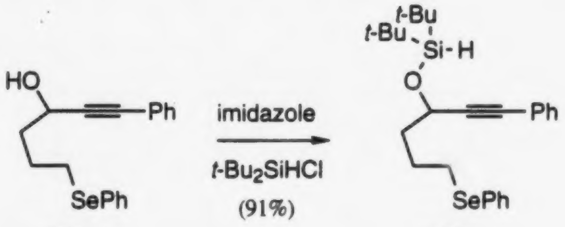
Scheme 79

hydride (**D**→**C**). Silicon radical **D** could also provoke[142] homolytic cleavage of the R–Se bond in substrate **A**, and consequently produce both selenide **E** and radical **B**. In this cyclic pathway (**B**→**D** + **A**→**E** + **B**), only catalytic amounts of the stannane reagent would be required. Finally, the product of the usual radical cyclization (**A**→**B**→**F**→**G**) is expected. However, none of these processes would fulfill our objective.

On the other hand, vinyl radical **F** could abstract the hydrogen atom from the silane protective group, leading to formation of silicon radical **H** with the desired control of stereochemistry at the exocyclic olefin. Then, this silicon radical could either be reduced by tin hydride (**H**→**I**), or could react with substrate **A** to give both selenide **J** and radical **B** in another cyclic process (**B**→**F**→**H** + **A**→**J** + **B**).

Although the rate of intramolecular hydride transfer of silanes is not known, we were confident that the radical cyclization, certainly in a 5-*exo-dig* situation, would be an important pathway.[144] Also, the fact that silicon rarely makes multiple bonds[145] should limit the radical fragmentation of the type found with the benzyl protective group (Table 2, and Introduction Scheme 25).

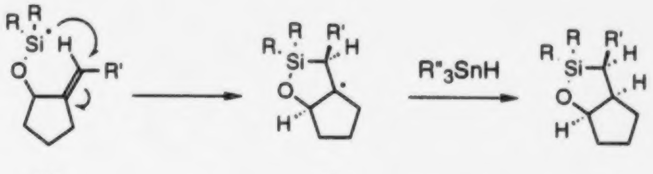
Fortunately, alcohol **269** had been prepared by us already (Scheme 66), and it was converted into silyl ether **309** by treatment with di-*tert*-butylchlorosilane[146,109a] and imidazole (Scheme 80).



269 **309**

Scheme 80

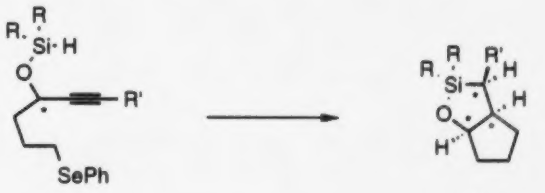
Treatment of a benzene solution of silyl ether **309** with triphenyltin hydride and AIBN (all reagents added at once) gave cyclic compound **G** or **I** (*ca*. 30%) (Scheme 79, R = *t*-Bu, R' = Ph), and another substance (26% yield) whose characteristics did not correspond to any of the predicted products of this reaction. This unknown compound, isolated as a single isomer (^{1}H NMR), had: (a) **no** signal attributed to an olefinic proton (*cf.* **G**, **I**, **J**); (b) **no** signal corresponding to a silicon hydride (*cf.* **C**, **G**, **I**); and also (c) **no** signal attributed to allylic protons. The logical conclusion from this data was that the exocyclic double bond and the silane Si–H bond have reacted together. Indeed, *the silicon radical, formed in the intramolecular radical transfer, had added in a 5-endo-trig fashion onto the double bond, to give bicyclic compound **L*** (Scheme 81).



H **K** **L**

Scheme 81

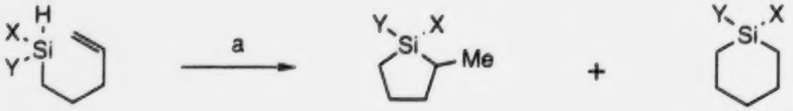
5-*Endo-trig* radical closure is rare (among chains composed of first-row elements[147,47c,47e]) and is disfavored by Baldwin's rules Beckwith's guidelines. The radical cyclization (**H→K**) occurred from the same face as the oxygen, dictating the relative stereochemistry at the carbon bearing the R' substituent. Finally, the carbon radical **K** was reduced by the stannane from the least hindered face of the molecule, to give the *cis* fused ring junction of bicyclic product **L** (Scheme 82). In this novel free radical reaction, three consecutive stereogenic centers (*) of compound **L** were totally controlled by the single stereogenic center (*) of substrate **A**.



A **L**

Scheme 82

Silicon radicals are known for their addition to olefins and acetylenes,[148,149] but only a few examples of silyl radical cyclization are known[148–150] (Scheme 83).



310a X = Me, Y = Ph	**311a** X = Me, Y = Ph (0.65%)	**312a** X = Me, Y = Ph (5.46%)
310b X = Ph, Y = Ph	**311b** X = Ph, Y = Ph (0.74%)	**312b** X = Ph, Y = Ph (6.1%)
310c X = *i*-Pr, Y = Cl	**311c** X = *i*-Pr, Y = Cl (3.94%)	**312c** X = *i*-Pr, Y = Cl (5.47%)
310d X = Me, Y = Cl	**311d** X = Me, Y = Cl (71.6%)	**312d** X = Me, Y = Cl (12.6%)

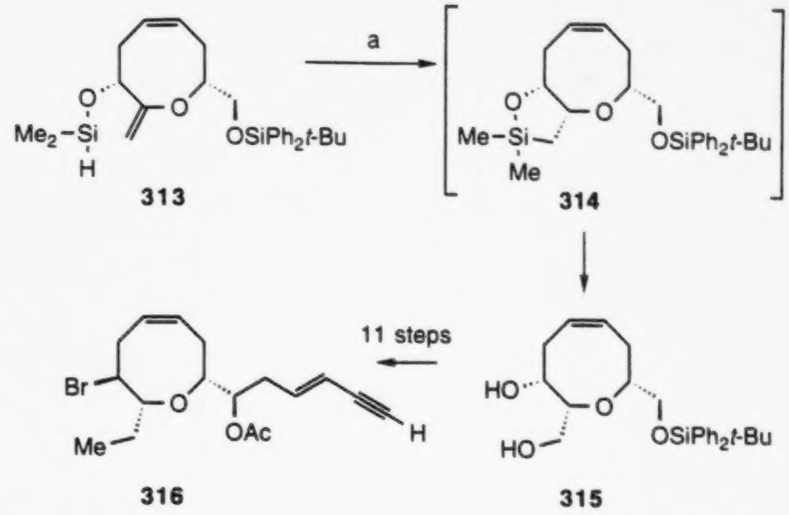
Scheme 83 *Reagents and conditions*: (a) (t-BuO)$_2$, 135 °C (reference 149)

We can enumerate some of the factors which make our new tandem radical reaction possible. In reactions of 5-hexenyl radicals, substitution of a carbon atom in the chain by silicon increased, in some cases, the ratio of product formed in a 6-*endo-trig* cyclization.[151] The rationale for this behavior invoked a longer C–Si bond length as compared with the C-C bond (1.872 Å versus 1.53 Å). Also, the tetrahedral geometry of the silicon radical might be beneficial in the orbital requirements of the 5-*endo-trig* cyclization.[150,152]

The new radical reaction (Schemes 79, 81 and 82) can be described as a 5-*exo-dig* radical cyclization (**A**→**B**→**F**), followed by a 1,5-hydrogen transfer (**F**→**H**), and terminated by an intramolecular radical hydrosilylation (**H**→**K**→**L**).

Intermolecular hydrosilylation[153] of unsaturated functional groups are known, and intramolecular variants of this reaction[154] have appeared more recently in organic synthesis. For example, this reaction (**313**→**314**) was successfully used in the elaboration of marine natural product (+)-laurencin[156] **316** (Scheme 84). In these methods, including the example shown, platinum or rhodium complex catalysts are used to trigger the annulation (**313**→**314**).

Mechanistic studies[156] of these methods have demonstrated that hydrosilylation under these conditions was reversible. Optically active catalysts were also used, giving variable ratios of asymmetric induction.[157]

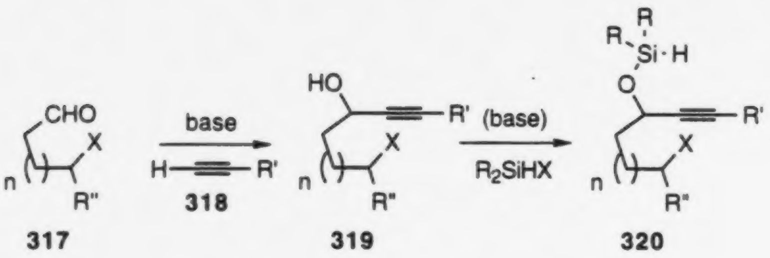


Scheme 84 *Reagents and conditions*: (a) 2% mol Pt{[(CH$_2$=CH)Me$_2$Si]$_2$O}$_2$, THF, reflux, 16 h, followed by EDTA·2Na·2H$_2$O–hexane, and then KOH–H$_2$O$_2$, 65% (reference 155c)

This interest in hydrosilylation and the use of other silicon centered reagents can be explained by the availability of convenient methods[158] for oxidative cleavage of the C–Si bond. In this functional group transformation, the C–Si bond is converted into a C–O bond with retention of the original stereochemistry of the C–Si bond (**314**→**315**, Scheme 84). Consequently, the silicon group serves as a masked hydroxyl group, and this transformation has been used in many examples.[159]

We undertook a study of our new radical reaction (Scheme 82), with the goal of finding some of its limitations, and in uncovering its possible synthetic applications. Three aspects of this reaction were investigated, and their influence on the chemical yields of the bicyclic compound was evaluated: (a) modification of substituents (R) in the silicon group; (b) modification of the acetylene substituent (R'); and (c) the use of various radical sources for the cyclization.

The radical cyclization precursors would be assembled in the following manner (Scheme 85): (a) addition of the acetylide **318** to an aldehyde (**317**→**319**), and (b) protection of the hydroxyl group as a silicon ether (**319**→**320**).



Scheme 85

Part 1: Modification of the Protective Group.

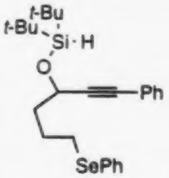
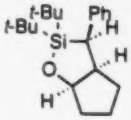
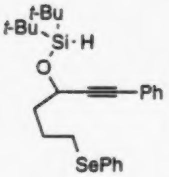
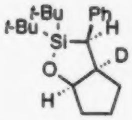
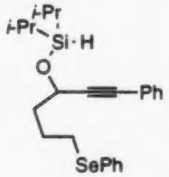
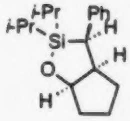
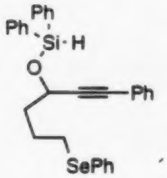
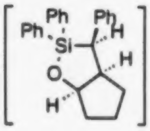
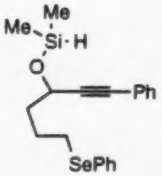
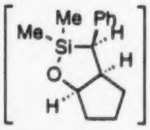
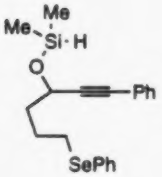
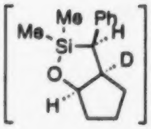
A first set of radical cyclization precursors was constructed, each member having two identical substituents in the silicon protective group to avoid the introduction of an additional stereogenic atom in the substrate. The results of these experiments are presented in Table 3.

For the radical cyclizations, a general procedure was adopted. The stannane (usually two equivalents) and radical initiator (0.5 equivalents of AIBN), both as solutions in benzene, were slowly added (*ca.* 2 h) to a refluxing solution of the selenide (or halide) in dry benzene. The final concentration of the substrate in these reactions was 5.0×10^{-3} M. These conditions were by no means the result of an extensive optimization: effects of temperature, solvent, radical initiator, final concentration and addition time still have to be explored.

The cyclization of selenide **309**, now using our standard conditions, gave bicyclic compound **321** in increased yield (Table 3, Entry 1).

In the next experiment, a deuterated tin hydride was used in order to locate the position of stannane reduction in the final compound (Table 3, Entry 2). In complete accordance with our predictions (Schemes 79 and 81), the deuterium was incorporated exclusively (^{1}H NMR and ^{2}H NMR) at the ring junction of bicyclic compound **322**.[160]

Table 3: Variation of the Protecting Group

	Protection (Yield^a)			Cyclization (Yield^a)		
Entry 1		**309**	91%		**321**	72%
Entry 2		**309**			**322**	64%
Entry 3		**323**	90%		**324**	35%
Entry 4		**325**	Quant.^{b}		**326**	c
Entry 5		**327**	Quant.^{b}		**328**	c
Entry 6		**327**			**329**	c

Key: (a) Yields not optimized; (b) Evaluated by ^{1}H NMR; (c) Although these intermediates could be isolated, we prefer to convert them directly into the corresponding diol **330–333** (see Table 4).

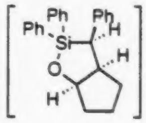
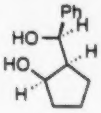
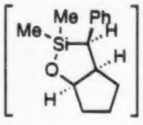
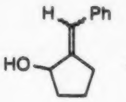
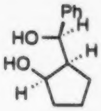
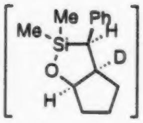
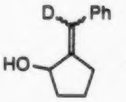
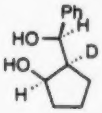
In a second example, alcohol **269** was treated with chlorodiisopropylsilane[109a,159m] and imidazole to give silane **323**. In this series, the yield of bicyclic compound **324** was lower than in the previous example (Table 3 , Entry 1).

Radical cyclization precursors **325** (Table 3, Entry 4) and **327** (Table 3, Entry 5) were obtained by reaction of alcohol **269** with chlorodiphenylsilane[109c,156b,157b] or tetramethyldisilazane, respectively.[109a,154c] Both silyl ethers were very sensitive to hydrolysis on silica gel and alumina, and could not be purified by chromatography. However, spectroscopic analysis of the reaction mixtures (^{1}H NMR) indicated that complete conversion was achieved in both cases. Consequently, the filtered reaction mixtures were used directly for the cyclization.

Both bicyclic compounds **326** and **328** could be isolated, but appeared to be formed in low yield. In our hands, these products were difficult to purify from stannane residues. Therefore, we decided to convert them into diol **330**, following Tamao's procedure[158a,159a] (Table 4). These results indicate a low overall yield for this three-step conversion.

Contrary to the clear origin of diols **330** and **333**, alcohols **331** and **332** could be formed in the hydrolysis of various precursors (Scheme 79, R = Me, R' = Ph): (a) normal radical cyclization without abstraction (**A→B→F→G**); (b) radical cyclization with intramolecular hydrogen abstraction (**F→H→I** or **J**); or (c) radical cyclization of the radical precursor which had been deprotected *in situ*. In the experiment in which the deuterated stannane was used (Entry 3), the results indicate that the vinyl hydrogen in alcohol **332** was provided by the external reducing agent, ruling out the second mode (b). In another experiment, the substrate **327** decomposed very slightly when a benzene solution of this compound was heated under reflux for a few hours. Assuming that the presence of stannane species in the reaction medium does not catalyze the decomposition of the protected radical precursors, this last result suggests that cyclic alcohols **331–332** were formed by radical cyclization of the protected substrate (pathway a).

Table 4: Tamao's Oxidation of Silicon Containing Bicyclic Compounds

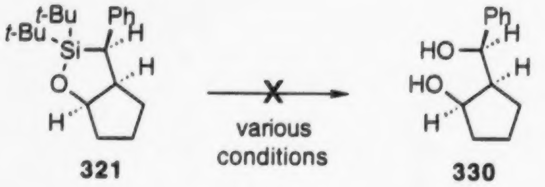
	Substrate[b]		Oxidation (Yield[a])					
Entry 1		**326**					**330**	14%
Entry 2		**328**		**331**	29%		**330**	27%[c]
Entry 3		**329**		**332**	38%		**333**	18%

Key: (a) Yields not optimized, and are reported over three chemical transformations. (b) Monocyclic products are also present in these reaction mixtures. (c) This example was latter repeated using a non-aqueous work up. See following discussion.

The result in the diphenylsilane series was somewhat disappointing. In general, aryl substitution in silanes increases the rate of intermolecular hydrogen abstraction by carbon radical.[148] From this information, we anticipated higher yields in this example. Consequently, factors other the relative stability of the silicon radical, formed during the intramolecular abstraction, regulate the efficiency of this reaction in the formation of the bicyclic compounds.

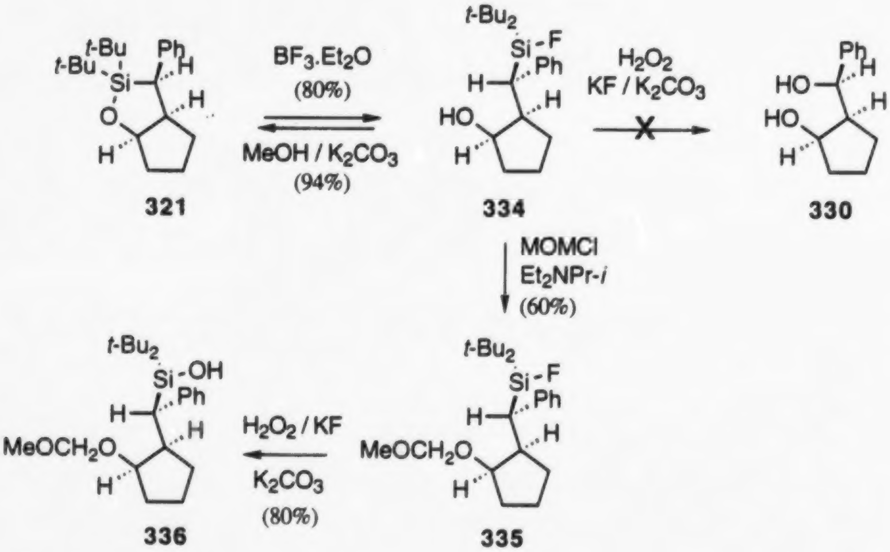
In these examples, the combined yields were acceptable. The material loss is most likely attributed to the final work up. In the dimethyl silane series, the overall yield (alcohol **331**, 45%; diol **330**, *ca*. 33%, results not reported in Table 4) was improved by the use of a non aqueous work up. However, the abstraction-cyclization process (Schemes 79 and 81, route **F→H→K→L**) was not as efficient as in the initial series.

Next, we tackled the conversion of bicyclic compound **321** into diol **330** (Scheme 86). Unfortunately, this substrate was reluctant to react under the most common oxidation



Scheme 86

conditions (acidic, neutral, or basic), and consequently failed to give any trace of diol **330**. Therefore, a stepwise approach for the oxidative cleavage of the Si–C bond was examined (Scheme 87). The silicon-containing ring was opened by treatment of the bicyclic compound **321** with boron trifluoride etherate,[143] and gave cleanly crystalline alcohol **334**, for which an X-ray analysis[161] was obtained. The chemical structure of alcohol **334** was therefore confirmed, and the relative stereochemistry of its three contiguous stereogenic atoms was in total agreement with our proposed mechanism.



Scheme 87

Also, bicyclic compound **321** was inert when treated with tetrabutylammonium fluoride.[143] This last result suggested that in more elaborate examples, other hydroxyl groups could possibly be protected as silyl ethers, which could be removed selectively without affecting the bicyclic system (R = *t*-Bu).

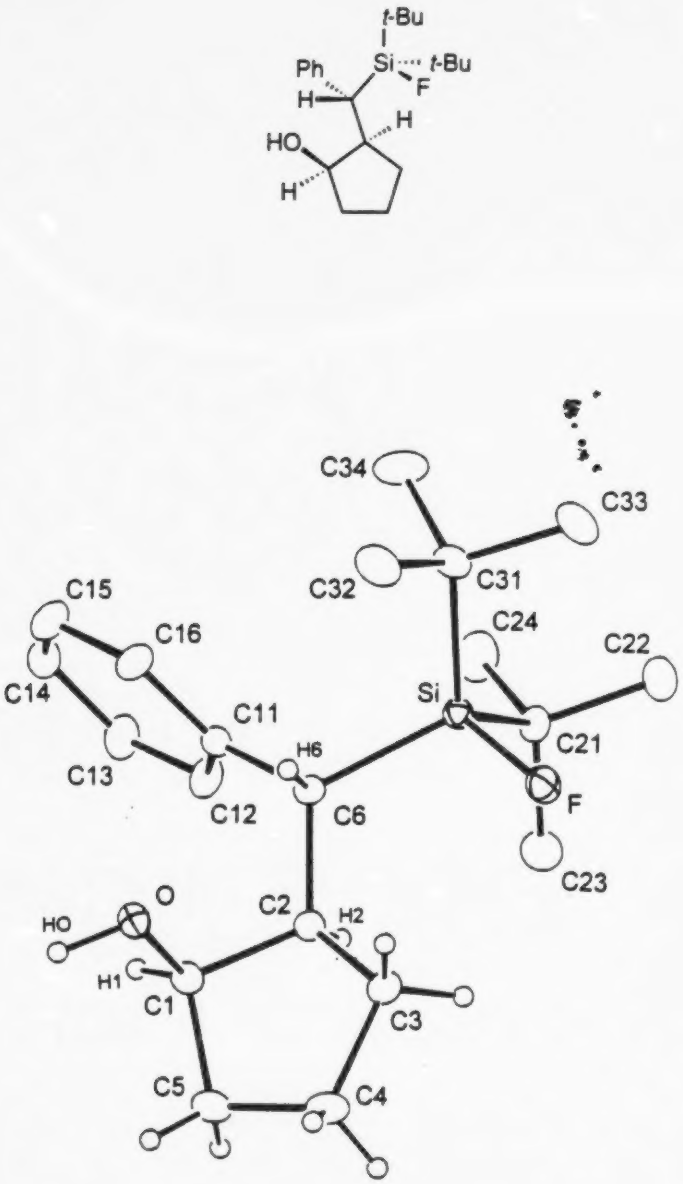
In a attempt to cleave the Si–C bond, fluoride **334** was subjected to Tamao's basic oxidation conditions, which gave exclusively (^{1}H NMR) bicyclic compound **321**, the silicon (Si–F) group being attacked by the alkoxide derived from the alcohol (Scheme 87). To confirm this result, fluoride **334** was dissolved in basic methanol and, within 45 minutes, bicyclic compound **321** was produced in excellent yield. This result might explain the apparent inertness of compound **321** to basic oxidation conditions: the fluoride **334**, which is expected to be formed during this reaction, would be immediately converted back into its precursor.

Since the presence of a free hydroxyl was problematic in this reaction, alcohol **334** was protected as its methoxymethyl ether **335**. Again, the oxidation (basic conditions) of this substrate failed, and silanol **336** was isolated. Similar behavior of Si–F containing groups during basic oxidation conditions has also been reported by Fuchs.[159l]

Increasing the electrophilicity of the di-*tert*-butyl silicon group by halogen substitution would not be useful, since all other halogens would be oxidized[158b] by hydrogen peroxide. Consequently, no other attempt was made to transform bicyclic compound **321** into diol **330**.

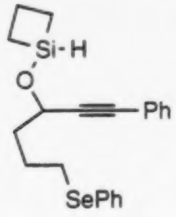
In these experiments (Table 3, Table 4), the silicon group having the largest substituent gave the best yield of the bicyclic compound (*t*-Bu > *i*-Pr ≈ Me ≈ Ph). These results are parallel to a previous conclusion that the cyclization of silicon radicals onto a terminal olefin produced more *endo* product as the size of the silicon substituents was increased[149] (Scheme 83).

Figure 1: Perspective View of Alcohol 334.

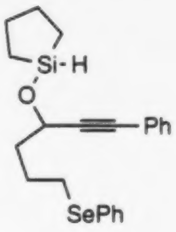


For future investigations, the behavior of various cyclic silicon protective groups[157b,158b] **337–339** in our new reaction, and subsequent derivatization would be worth considering.

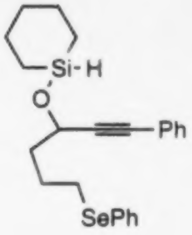
337



338



339



Part 2: Modifications of the acetylenes

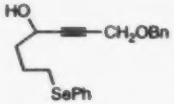
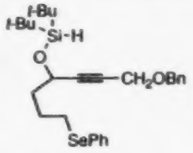
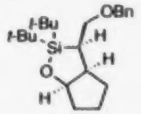
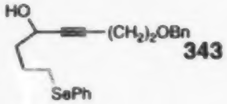
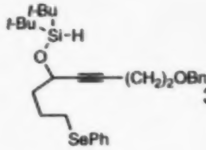
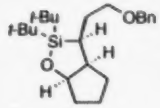
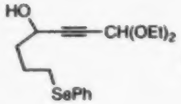
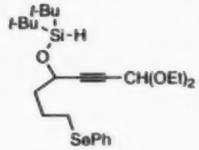
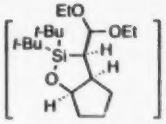
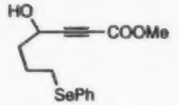
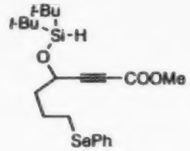
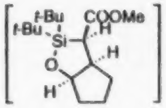
In the second aspect of our investigation, the substituents on the acetylene were modified, while other parameters (initial 5-*exo-dig* cyclization and the use of di-*tert*-butyl silyl protective group) were kept constant. Also, the use of various oxidation levels in the radical acceptor was investigated (Table 5): a protected alcohol (Entry 1), a acetal functional group (Entry 3), and an ester group (Entry 4).

Alcohols **340**, **343**, and **346** (Table 5, Entries 1–3) were obtained by the coupling of aldehyde **267** (Scheme 66) with the required acetylenes, easily prepared from 2-propyn-1-ol[162] (Entry 1) or 4-butyn-1-ol (Entry 2), or with propionaldehyde diethyl acetal[109d] (Entry 3). A slight modification to our procedure was necessary for the preparation of alcohol **349** (Entry 4), which required the use of lithium diisopropylamide as a base to accommodate the ester functional group.[163] Each alcohol was subsequently converted to its corresponding di-*tert*-butyl silyl ether.

Radical cyclization of compound **341** gave bicyclic compound **342** (Table 5, Entry 1), in a slightly lower yield than in the original series (Table 3, Entry 1).

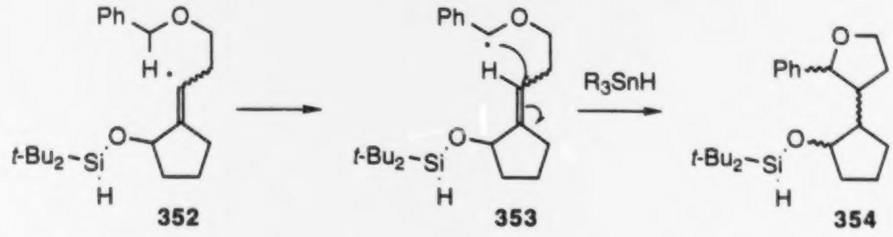
In the next substrate, the carbon chain between the oxygen functional group and the terminal acetylene was elongated by one unit (Entry 2). In this example, the 1,5- hydrogen

Table 5: Variation of the Acetylenes

	Coupling (Yield^a)			Protection (Yield^a)			Cyclization (Yield^a)		
Entry 1		**340**	71%		**341**	92%		**342**	57%
Entry 2		**343**	71%		**344**	95%		**345**	57%
Entry 3		**346**	80%		**347**	93%		**348**	b
Entry 4		**349**	86%		**350**	84%		**351**	b

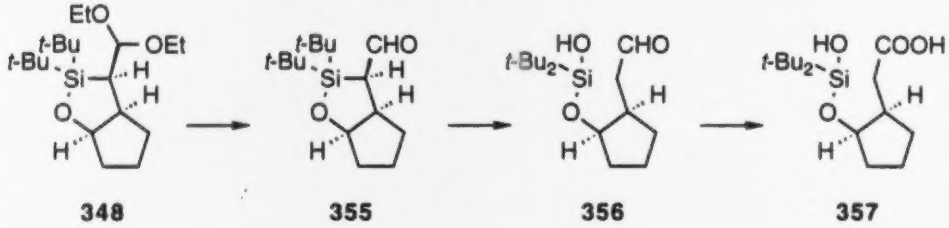
Key: (a) No yields optimized; (b) See following discussion.

abstraction could also occur at the activated benzyl ether contained in the acetylene chain. Indeed, radical cyclization of silyl ether **344** produced compound **345**, and a mixture of compounds **354** in *ca.* 19% yield[164] (Scheme 88). Although this last pathway was minor in this particular example, consideration of this side reaction must be made in future applications of this method.



Scheme 88

The radical cyclization of acetal **347** (Entry 3) was more problematic than anticipated. In our hands, the desired bicyclic compound **348** could not be isolated in pure form. In all experiments, aldehyde **355** was isolated (^{1}H NMR, *ca.* 30%), or was present with compound **348** as an inseparable mixture. The crude ^{1}H NMR of the cyclization reaction gave no indication of the presence of an aldehyde. Therefore, partial hydrolysis of the acetal must have occurred during purification by chromatography on silica gel.



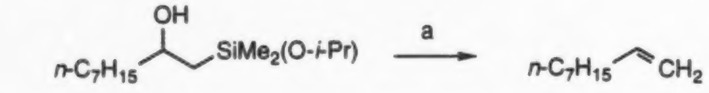
Scheme 89

In order to complete the conversion of acetal **348** into aldehyde **355**, a solution of the above mixture was stirred at room temperature with moist silica gel. Once again, a mixture of two new compounds was formed, one being an aldehyde (probably ring opened aldehyde **356**) and an unknown product. Larson[165] has reported similar cleavage of a C–Si bond assisted by β-carbonyl groups.

Upon leaving this second mixture in deuterated chloroform at room temperature (*ca.* 6-8 weeks, by which time the solvent had evaporated), a single compound was observed, and was later identified (although not fully characterized) as carboxylic acid **357**. It was formed in very low overall yield (*ca.* 10% from **348**). There is a strong possibility that a substantial amount of acid **357** was lost during the work up of the hydrolysis reaction (Scheme 89, **348** + **355**→**356** + **357**). A more controlled conversion of aldehyde **348** into open ring aldehyde **355** would be required in the future, if the experiment is repeated.

Equally, the cyclization of ester-containing selenide **350** (Entry 4) gave a disappointing result. Although the desired bicyclic compound **351** was formed during the reaction (^{1}H NMR), the difficulty of detection (tlc) of the desired product by using common reagents (vanillin-H_2SO_4, anisaldehyde–H_2SO_4, PMA, H_2SO_4) made its purification complicated. The use of an ester having a chromophore (benzene ring) is suggested for further work.

Cleavage of the Si–C bond in β-hydroxysilyl groups has precedent,[159b] as demonstrated by Scheme 90, and is an integral part of the classic Peterson reaction.

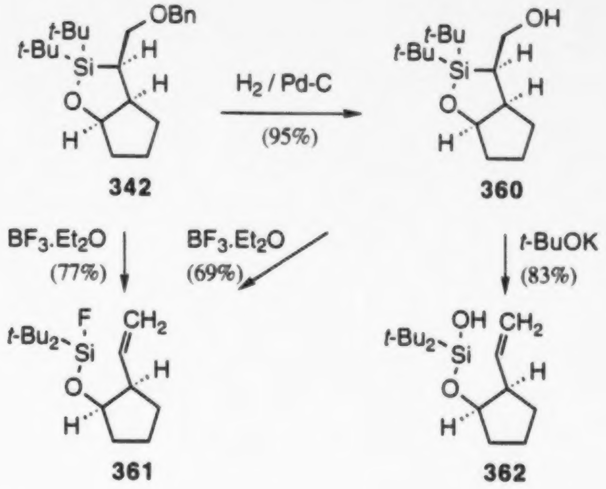


358 **359**

Scheme 90 *Reagents and conditions*: (a) $BF_3 \cdot Et_2O$, 0 °C, 2 h, 93% (reference 159b)

Bicyclic compound **342** (Table 5, Entry 2) had all the required elements to attempt this Si–C bond cleavage, despite the loss of one stereogenic center in this transformation.

Hydrogenolysis[166] of the benzyl ether **342** produced the expected alcohol **360** (Scheme 91). Then, treatment of a solution of alcohol **360** in dichloromethane with

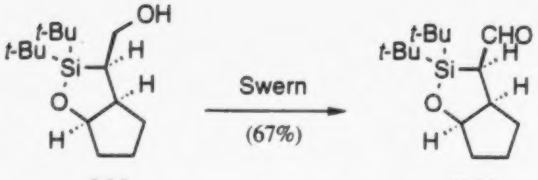


Scheme 91

boron trifluoride etherate gave exclusively fluoride **361**. More interestingly, compound **342**, when treated with the same Lewis acid, gave directly fluoride **361** in similar yield. This latter result has a significant consequence: the cleavage of the Si–C bond in bicyclic compounds containing any other ether protective group should also be easy.

The same Si–C bond cleavage was also achieved by treatment of a solution of alcohol **360** with potassium *tert*-butoxide, giving silanol **362**.[169] These two complementary methods, one using a Lewis acid, the other a base, provide some versatility for future uses of the β hydroxysilicon moiety.

Aldehyde **355** could be obtained by oxidation of alcohol **360**. Although pyridinium chlorochromate[167] produced a mixture of products, Swern[168] oxidation gave cleanly aldehyde **355**, without epimerization (^{1}H NMR) of the adjacent center (Scheme 92). Besides the unexpected conversion of aldehyde **355** into carboxylic acid **357** (Scheme 89), exploratory work on the controlled cleavage of the Si–C bond of the northern ring was inconclusive.



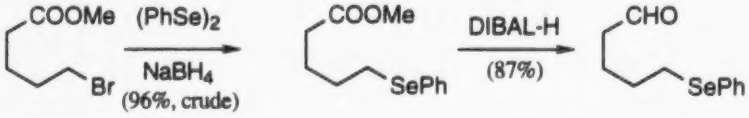
360 **355**

Scheme 92

Part 3: Various Radical Sources

Generalization of our new radical reaction would not be complete without the investigation of various cyclization modes, such as the formation of 6-membered rings, or the cyclization of vinyl, aryl, secondary or allyl radicals. To deal with these aspects, appropriate radical cyclization precursors were assembled following our general strategy (Scheme 85), and the results of these experiments are shown in Table 6.

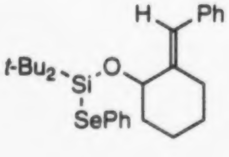
Aldehyde **365**, required for the synthesis of alcohol **366** (Entry 1), was readily accessible from methyl 5-bromovalerate[109a] **363** (Scheme 93).



363 **364** **365**

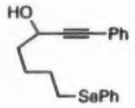
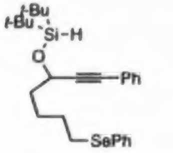
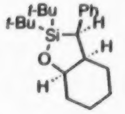
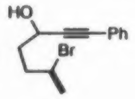
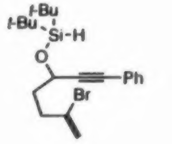
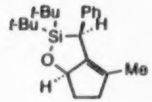
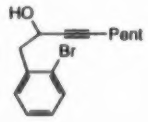
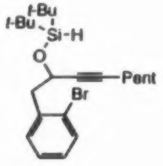
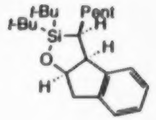
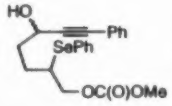
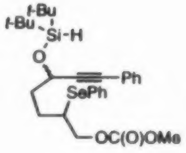
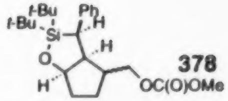
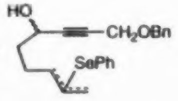
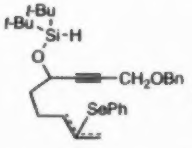
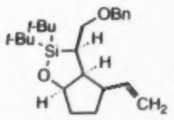
Scheme 93

Radical cyclization (6-*exo-dig*) of selenide **367** gave bicyclic compound **368**, in much lower yield than the original (5-*exo-dig*) series (Table 3, Entry 1). Also, some selenide **369** (*ca.* 25%) was isolated in this reaction, but was not fully characterized.



369

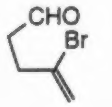
Table 6: Variation of the Radical Sources

	Coupling (Yield^a)			Protection (Yield^a)			Cyclization (Yield^a)		
Entry 1		**366**	75%		**367**	79%		**368**	24%^{b}
Entry 2		**370**	53%^{c}		**371**	88%		**372**	46%^{d}
Entry 3		**373**	65%		**374**	88%		**375**	91%
Entry 4		**376**	69%		**377**	88%		**378**	67%^{e}
Entry 5		**379**	66%		**380**	77%		**381**	30%^{f}

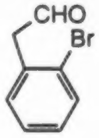
Key: (a) No yields were optimized; (b) Selenide **366** was also isolated; (c) Yield from alcohol (over two steps); (d) Various yields and results (sometime mixtures);(e) Mixture 3:7 *cis-trans*; (f) Mixture of isomers 3:7, with 10% unknown compound.

Despite the low efficiency, our method might be the only way to make benz[*d*][1,2]-oxasilole such as compound **368**, since Bergens[157b] reported the failure of the metal complex method in the synthesis of a related compound.

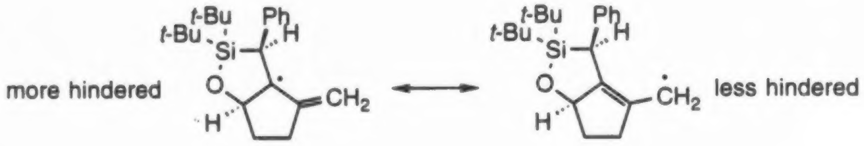
Next, the radical cyclization of vinyl (Entry 2) and aryl (Entry 3) radicals were studied. Fortunately, both aldehyde[170] **382** and aldehyde[171] **383** required for the synthesis of radical precursors **371** and **374** were known, and they were prepared following the available procedures. Radical cyclization of vinyl bromide **371** gave mainly bicyclic compound **372**, in which the double bond was located at the ring junction. The 5-*endo-dig* cyclization on the diene led to the formation of the allylic radical, represented by resonance structures **384** and **385**. The stannane approached preferentially from the least hindered site of the radical, resulting in formation of the tetrasubstituted olefin. The bicyclic compound **372** was sometimes contaminated by another compound, whose structure was not elucidated. Moreover, the results of this cyclization were difficult to reproduce.[172]



382



383

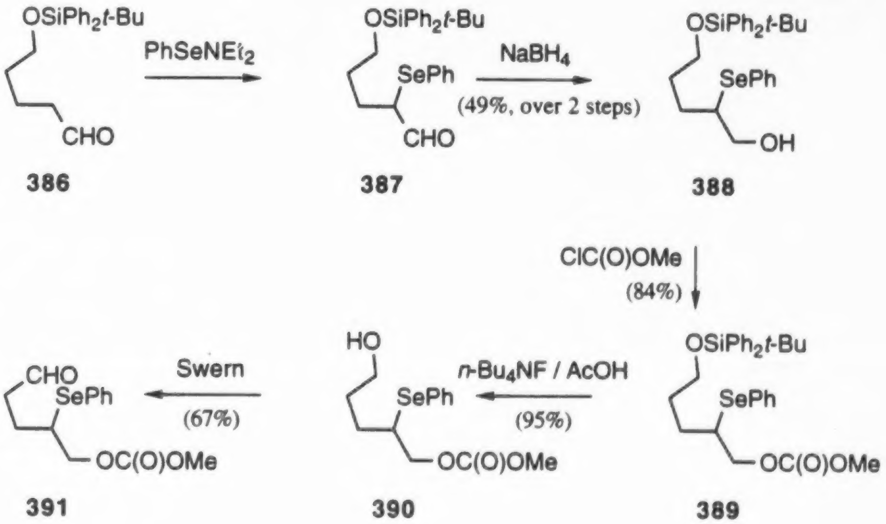


384 **385**

Curran[48a] reported similar variable behavior of vinyl bromides in radical translocation. He suggested two solutions to this problem: the use of vinyl iodide radical precursors, or the use of Stork's radical cyclization method.[173] Our substrate was treated under these latter conditions, but no apparent advantage resulted from this single experiment. The corresponding vinyl iodide of radical precursor **371** was not prepared.

In our next example (Entry 3), both the radical source and the acetylene carbon chain were modified. As in an earlier example (Table 5, Entry 2), the possibility of intramolecular abstraction by the vinyl radical of a hydrogen from the carbon chain was explored[55g] (see Scheme 88). Cyclization of aryl bromide **374** gave very cleanly tricyclic compound **375**. No other compounds were isolated in the cyclization of substrate **374**.

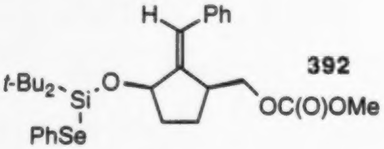
Silyl ether **377** (Entry 4) was selected as an example of a secondary radical cyclization. The oxygen-containing group, located at the terminal position had two functions: to assist in the introduction of the radical source (PhSe group), and for further chemical transformations on the expected bicyclic structure. The construction of the aldehyde required for the coupling reaction is summarized in Scheme 94.



Scheme 94

Aldehyde **386**[174] was selenated,[175] and the purified compound **387**, still contaminated by some unreacted aldehyde **386**, was reduced[176] by sodium borohydride to the corresponding alcohol **388**. The free hydroxyl group was protected as carbonate **389**,[177] the silicon protective group was then removed by treatment with tetrabutylammonium fluoride,[178] and resulting alcohol **390** was converted to aldehyde **391** by performing a Swern[168] oxidation.

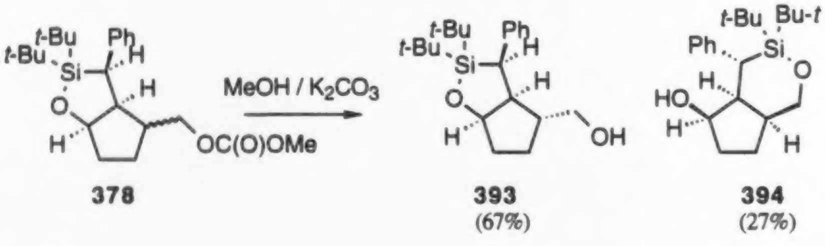
Coupling of aldehyde **391** with phenyl acetylene gave alcohols **376** as a mixture of epimers. The formation of diastereomers in the coupling reaction was of no consequence since the stereogenicity of the carbon that bears the radical source will be destroyed during radical formation. Alcohols **376** were finally converted into silyl ethers **377**, and the radical cyclization of this mixture gave monocyclic selenide **392** as a single isomer,[179] and bicyclic compounds **378**, obtained as a 3:7 mixture of inseparable (tlc, silica) isomers.



392

The relative stereochemistry of both major and minor products of mixture **378** was not established at this stage, but was later assigned.

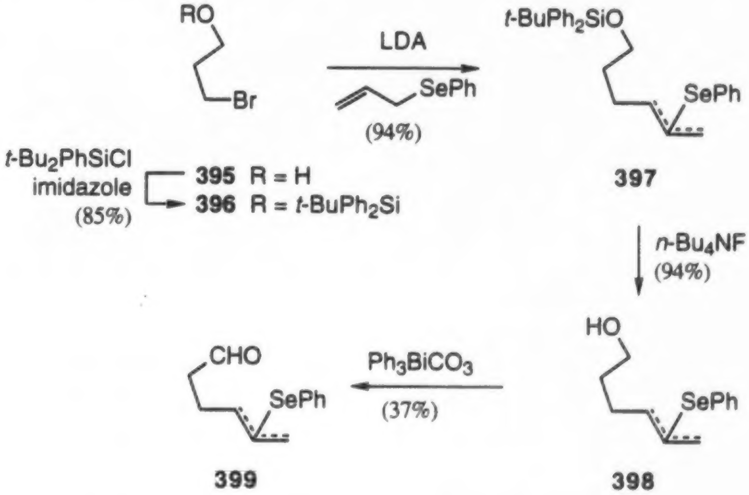
Deprotection of the hydroxyl group was performed with the expectation that the corresponding alcohols would be easier to separate. Treatment of a methanolic solution of mixture **378** with potassium carbonate gave the expected the *trans*-alcohol **393**, and surprisingly, the rearranged alcohol **394** (Scheme 95), which structure assignment is based on some coupling constants of the ^{1}H NMR spectrum. These compounds were easily separated, the primary alcohol having more affinity to the silica gel than the more hindered secondary alcohol.



Scheme 95

This result also provided additional information: the *trans*-isomer was the major component of mixture **378**. The rearranged compound **394**, derived only from the minor *cis* isomer, was formed by intramolecular attack by the hydroxyl group (or its corresponding alkoxide) on the silicon containing group, via the possible formation of a pentavalent intermediate,[136a] which then collapsed to give the isolated compound. A similar intramolecular migration of a silicon ether was reported in a prostaglandin synthesis.[180] However, our example is characterized in the fact that the silicon group is solidly anchored to the molecular skeleton by a strong Si–C bond.

As our last example of this study, a model for the cyclization of an allylic radical was constructed (Table 6, Entry 5). An efficient method, developed by Reich,[181] was used to assemble the required allylic selenide portion of the radical cyclization precursor



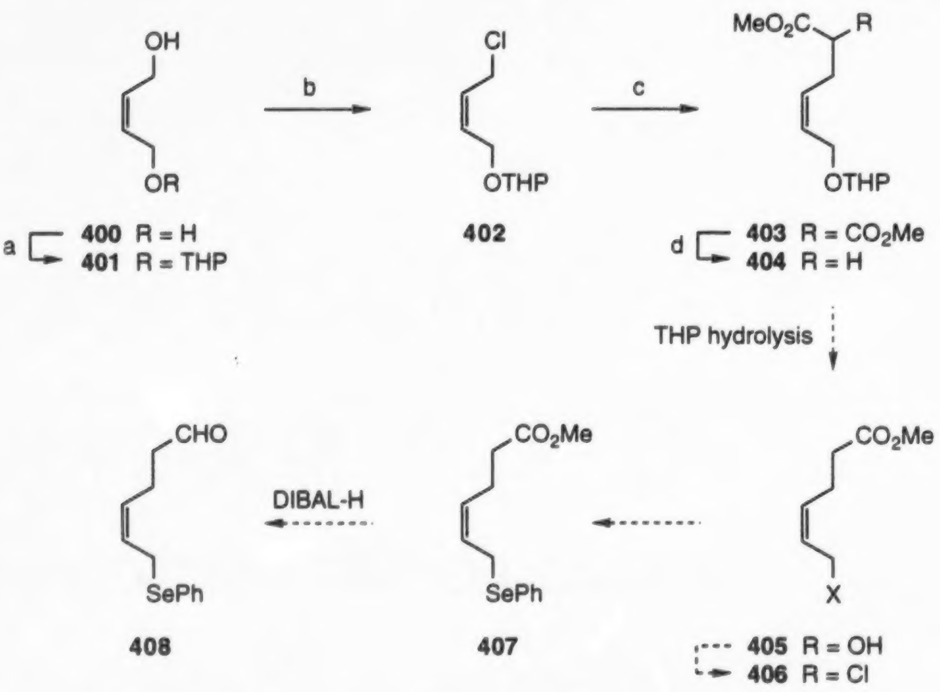
Scheme 96

380 (Scheme 96). 3-Bromo-1-propanol **395** was protected as its *tert*-butyldiphenylsilyl ether **396**, and a nucleophilic substitution of the primary bromide by the anion of allyl phenyl selenide[182] gave the allylic selenides **397** as a mixture of isomers,[183] all suitable for the subsequent formation of the allylic radical. The silicon group was then removed, giving a mixture of alcohols **398**.

Oxidation of alcohols **398** proved to be more difficult than expected. Swern[168] or Corey-Kim[184,185] oxidation, or treatment with either 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[186] or pyridinium dichromate[186] failed, or gave poor yields of the desired aldehydes **399**. Triphenylbismuth carbonate[187] was the best reagent we tried for this oxidation, but it gave only 37% yield of aldehyde **399**.

The radical cyclization precursor **380** was elaborated once again following our simple method. Its cyclization gave a mixture (*ca.* 3:1) of bicyclic compounds **381**, having the expected terminal olefin. At this stage, it was not necessary to determine the stereochemistry of the vinyl pendant in these compounds (see further discussion).

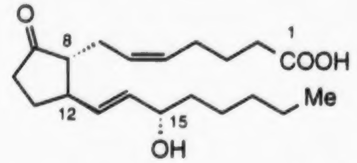
Difficulty in the interpretation of spectroscopic data (both ^{1}H and ^{13}C NMR)



Scheme 97 *Reagents and conditions*: (a) DHP, *p*-TsOH, CH_2Cl_2, 0 °C, 1.5 h, rt, 1.5 h, 53%; (b) LiCl, *s*-collidine, CH_3SO_2Cl, DMF, 0 °C, 15 min, rt, 1 h, 83%; (c) $CH_2(CO_2Me)_2$, K_2CO_3, DMF/THF (1:1), reflux, 13 h, 89%; (d) NaCN, H_2O, DMSO, 140–145 °C, 5 h, 53% (reference 188)

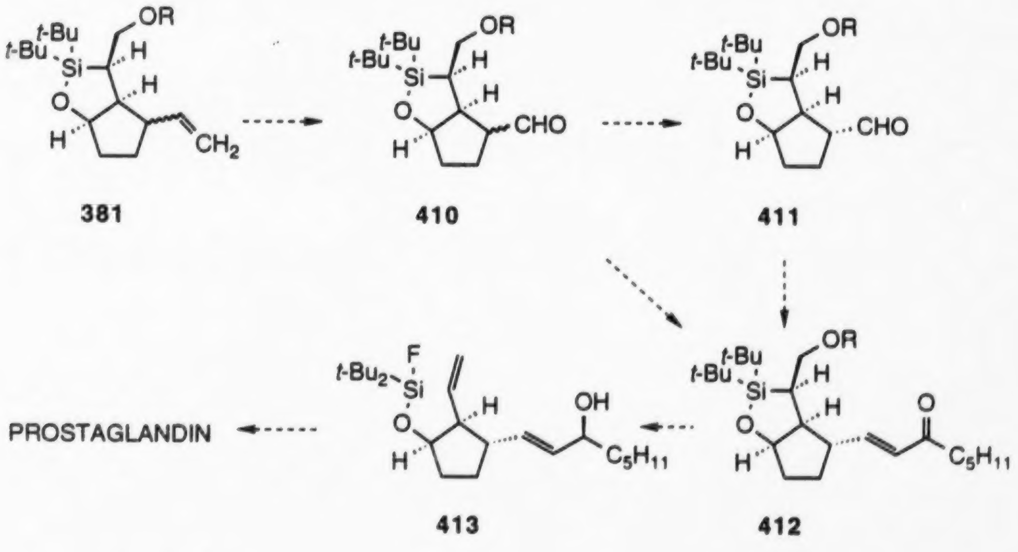
generated in this last series led us to suggest, for future work, an alternative route for the synthesis of a different aldehyde containing an allyl selenide portion (Scheme 97). The transformation of *cis*-2-butene-1,4-diol **400** into intermediate **404** is known,[188] and the remaining chemical steps for its conversion into aldehyde **408** appear to be straightforward. Although this new route has more steps than our previous route, the problematic oxidation step will be avoided.

Our interest in the allylic radical cyclization was initiated by possible application of our new method to the synthesis of 11-deoxy prostaglandins (e.g. compound **409**).



409 11-DEOXY PGE_2

Many extensive reviews[189] have been published on prostaglandin synthesis, and there is some indication that the functional groups required for the synthesis of a prostaglandin like structure are present in bicyclic compound **381** (Scheme 98). Cleavage of the exocyclic double bond[190] would give a mixture of aldehydes **410** which would be epimerized,[191]

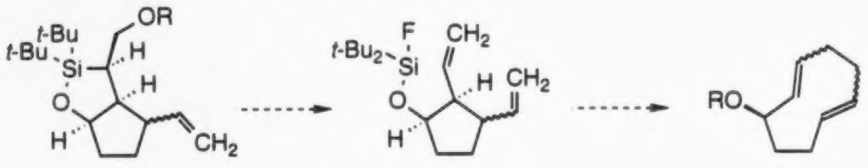


Scheme 98

leading to the formation of the desired *trans* aldehyde **411**. Chain elongation would be performed by a Wittig reaction during which epimerization could also occur, allowing the direct use of the mixture of aldehydes **411**.

The conversion of alcohol **413** into a suitable precursor in which the second chain elongation would be allowed (Wittig type), could be more problematic. Finally, our strategy for the construction of the radical cyclization precursor would have to be modified to allow synthesis of the specific enantiomer required.

This last series could also be used in the construction of medium sized rings by Cope rearrangement of dienes **415** (Scheme 99).

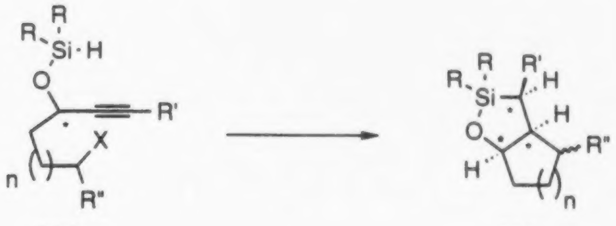


381 **414** **415**

Scheme 99

Conclusions

Our work on the use of intramolecular hydrogen abstraction led us to the invention of a new radical rearrangement (Scheme 100). In this remarkable tandem reaction, three contiguous stereogenic centers (*) were controlled by the propargylic hydroxyl group.



320 **416**

Scheme 100

The initial investigation of this reaction indicated that the transformation is general, although the yields are influenced by the type of radical source, and the substrate substituents, either in the acetylenic chain or in the silicon protective group. Other factors governing this reaction still have to be explored.

This reaction opens an unexplored area of radical chemistry,in which a radical source and a hydrogen atom source are located in the same molecule. Other atoms than silicon have still to be explored.

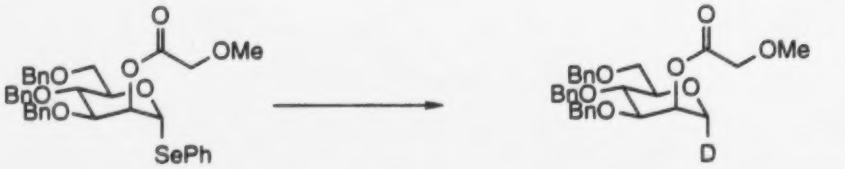
III EXPERIMENTAL

General Procedures. The same general procedures described in Chapter 1 apply with the following additions: Neutral alumina (aluminium oxide) was Canmag 507c (Brockmann Number: 1). Dimethyl sulfoxide (DMSO), hexane, pentane, and diisopropylamine were distilled from CaH_2. Acetone (reagent grade) was used in reactions without purification.

^2H NMR spectra were recorded on Bruker WH-400 (at 61.423 MHz) instrument in the specified solvent (non-deuterated), unlocked and without decoupling.

General Procedure for Radical Reduction of Mannosyl Selenides. The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser that was sealed with a rubber septum. The system was flushed with Ar for 5-10 min, and dry PhH was injected. The solution was refluxed, and separate solutions of Ph_3SnD[110] and AIBN in PhH were injected simultaneously by syringe pump over 6–9 h. Refluxing was continued for an arbitrary period of 6–9 h after the addition. The reaction mixture was cooled, and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

[1-$^2H_1$]-1,5-Anhydro-3,4,5-tri-*O*-benzyl-2-methoxyacetyl-D-mannitol (231).

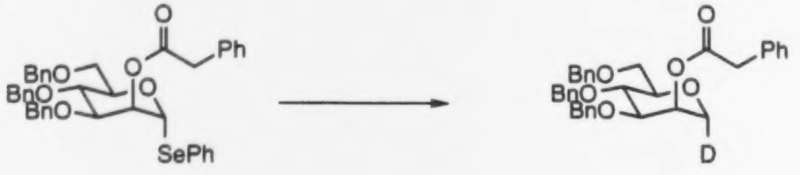


229 **231**

The general procedure for reduction of mannosyl selenides was followed, using selenide **229** (25.5 mg, 0.039 mmol) in PhH (3 mL), Ph_3SnD (20 mg, 0.069 mmol) in

PhH (1 mL), AIBN (*ca.* 3 mg) in PhH (1 mL), with an addition time of 6 h, and a reflux period of 12 h after the addition. After work up, flash chromatography over silica gel (1 × 7 cm), using increasing amounts of EtOAc in hexanes (from 15 to 50%), gave reduced product **231** (12.9 mg, 66%) as a thick oil: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.36–3.48 (m, including s at δ 3.52, 4 H), 3.50–3.60 (m, *ca.* 0.10 H), 3.63–3.70 (m, 4 H), 4.02–4.09 (m, 1 H), 4.16 (s. 2 H), 4.46–4.93 (series of d, 6 H), 5.50 (dd, *J* = 3.0, 2.0 Hz, 1 H), 7.09–7.42 (m, 15 H).

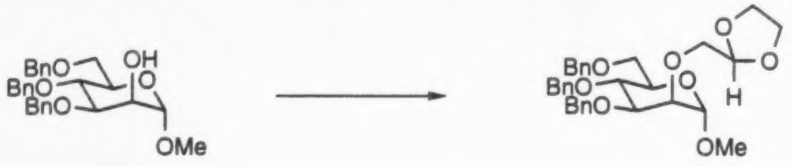
[1-^{2}H$_{1}$]-1,5-Anhydro-3,4,5-tri-*O*-benzyl-2-phenylacetyl-D-mannitol (232).



230 **232**

The general procedure for reduction of mannosyl selenides was followed, using selenide **230** (38.1 mg, 0.054 mmol) in PhH (6 mL), Ph$_3$SnD (31 mg, 0.088 mmol) in PhH (1.5 mL), AIBN (*ca.* 3 mg) in PhH (1.5 mL), with an addition time of 9 h, and a reflux period of 6 h after the addition. After work up, flash chromatography over silica gel (1 × 7 cm), using increasing amounts of EtOAc in hexanes (from 10 to 20%), gave reduced product **232** (8.0 mg, 27%) as a thick oil: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.38–3.46 (, 1 H), 3.50–3.60 (m, *ca* 0.15 H), 3.61–3.80 (m. 6 H), 4.07 (d, *J* = 2.0 Hz, 1 H), 4.44–4.88 (series of d, 6 H), 5.44 (dd, *J* = 3.5, 2.0 Hz, 1 H), 7.13–7.46 (m, 20 H).

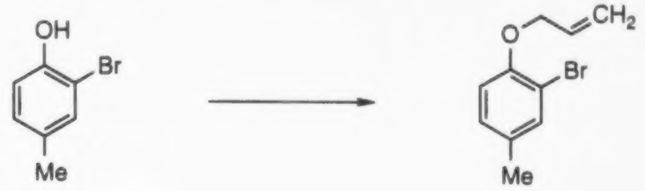
Protection of methyl 3,4,5-tri-*O*-benzyl-α-D-mannopyranoside (228).



228 **237**

NaH (32 mg, 60% dispersion in mineral oil, 0.80 mmol) and NaI (110 mg, 1.38 mmol) were added to stirred mixture of methyl mannoside[114] **228** (64 mg, 0.138 mmol) and 2-bromomethyl-1,3-dioxolane[109a,113] **236** (230 mg, 1.38 mmol) in dry DMSO (2 mL). The mixture was stirred at room temperature overnight. At that stage, the reaction was not complete [tlc, silica, EtOAc–hexanes (1:2)]. More reagents were added (NaH, NaI, the same amounts as before), and the mixture was heated at 70 °C overnight. The mixture was cooled to room temperature, water (25 mL) was added, and the resulting mixture was extracted with $CHCl_3$ (1 × 25 mL, 2 × 10 mL). The combined organic layers were washed with water (1 × 25 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.8 × 11 cm), using 1:2 EtOAc–hexanes, gave mannoside **237** (48 mg, 63%) as a thick oil: FTIR ($CHCl_3$ cast) 2900, 1492, 1447, 1359, 1026, 1085, 738, 598 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.39 (s, 3 H), 3.65–4.08 (m, 12 H), 4.49–4.93 (m, 7 H), 5.12 (t, J = 3.5 Hz, 1 H), 7.17–7.24 (m, 2 H), 7.26–7.46 (m, 13 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 54.72 (q'), 65.05 (t'), 65.10 (t'), 69.32 (t'), 71.65 (d'), 72.07 (t'), 72.33 (t'), 73.35 (t'), 74.79 (d'), 75.01 (t'), 76.63 (d'), 76.76 (t'), 77.06 (t'), 77.48 (t'), 80.14 (d'), 99.20 (d'), 103.17 (d'), 127.45 (d'), 127.51 (d'), 127.65 (d'), 127.78 (d'), 127.82 (d'), 127.89 (d'), 128.26 (d'), 128.32 (d'), 128.51 (d'), 138.42 (s'), 138.54 (s'), 138.57 (s'); exact mass *m/z* calcd for $C_{25}H_{31}O_8$ $(M - C_7H_7)^+$ 459.2018, found 459.2023; mass (CI) *m/z* calcd for $C_{32}H_{42}O_8N$ $(M + 18)^+$ 568, found 568.

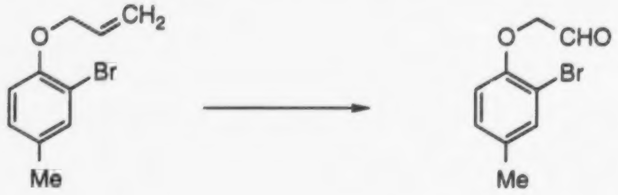
2-Bromo-4-methyl-1-allyloxybenzene (417).



241 **417**

NaH (60% dispersion in oil, 1.27 g, 31.8 mmol) was added in 10 portions over 5 min to a stirred solution of bromophenol[115] **241** (5.40 g, 28.9 mmol) and allyl bromide (5.20 g, 43.0 mmol) in a 1:4 mixture of DMF–THF (100 mL). Stirring was continued at room temperature for 24 h. Water (200 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (20 × 5 cm), using increasing amounts of Et_2O in hexane (from 0% to 5%), gave allyl ether **417** (6.13 g, 93%) as a pure [^{1}H NMR, (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 3000, 1495, 1285, 1257, 1052, 801 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 3 H), 4.57 (dt, J = 5.0, 1.5 Hz, 2 H), 5.30 (dq, J = 10.5, 1.5 Hz, 1 H), 5.47 (dq, J = 17.5, 1.5 Hz, 1 H), 6.07 (ddt, J = 17.5, 5.0, 1.5 Hz, 1 H), 6.78 (d, J = 8,5 Hz, 1 H), 7.03 (ddd, J = 8.5, 2.0, 0.5 Hz, 1 H), 7.37 (dd, J = 2.0, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.15 (q'), 69.88 (t'), 112.06 (s'), 113.70 (d'), 117.55 (t'), 128.76 (d'), 131.71 (s'), 132.86 (d'), 133.77 (d'), 152.82 (s'); exact mass *m/z* calcd for $C_{10}H_{11}{}^{81}BrO$ 227.99773, found 227.9975.

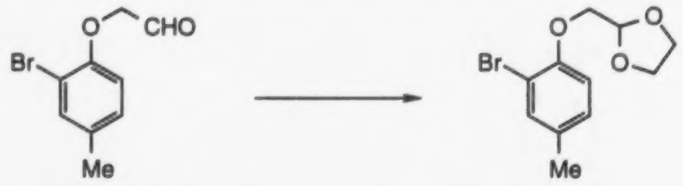
(2-Bromo-4-methylphenyloxy)-1-acetaldehyde (418).



417 **418**

An ozone-oxygen stream was bubbled through a stirred and cooled (-78 °C) solution of **417** (1.14 g, 5.00 mmol) in dry CH_2Cl_2 (100 mL) until the solution turned faintly purple.[192] Stirring was continued at -78 °C for 5 min (persistence of the purple color), and Ar was bubbled through the solution for 5 min. Ph_3P (3.30 g, 12.5 mmol) was added, stirring was maintained at -78 °C for 30 min, the cold bath was removed, and stirring was continued at room temperature overnight under Ar. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.7 × 18 cm), using increasing amount of EtOAc in hexane (from 20% to 30%), gave aldehyde **418** (1.10 g, 96%) as a white solid. This compound appeared to decompose rapidly [^{1}H NMR], and was used directly without full characterization: FTIR ($CHCl_3$ cast) 3000, 1496, 1286, 1257, 1059 cm^{-1}; exact mass *m/z* calcd for $C_9H_9{}^{81}BrO_2$ 229.9765, found 229.9777. Anal. Calcd for $C_9H_9BrO_2$, 47.19; H, 3.96; Br, 34.88. Found: C, 47.30; H, 3.73; Br, 35.02.

[2-Bromo-4-methylphenyloxy)methyl]-1,3-dioxolane (243).

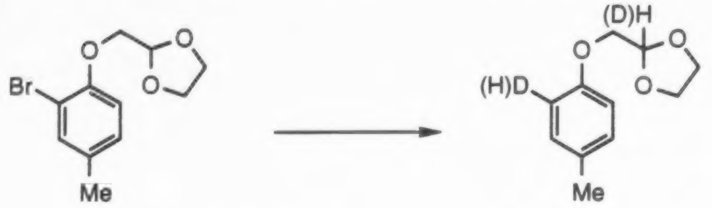


418 **243**

p-TsOH·H_2O (*ca.* 10 mg) was added to a stirred solution of aldehyde **418** (2.37 g, 10.3 mmol) and ethylene glycol (1.00 g, 16.1 mmol) in dry PhH (50 mL). The flask was equipped with an addition funnel (60 mL) which was filled with oven-dried molecular sieves (3Å, *ca.* 15 g). The funnel was equipped with a condenser, and the mixture was heated at 80 °C for 24 h. The mixture was cooled to room temperature, and the solvent was evaporated. Flash chromatography of the residue over silica gel (2.8 × 15 cm), using 3:7 EtOAc–hexane, gave bromide **243** (2.54 g, 90 %) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2888, 1497, 1287, 1257, 1148, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3 H), 3.93–4.00 (m, 2 H), 4.04 (d, J = 3.5 Hz, 2 H), 4.08–4.15 (m, 2 H), 5.34 (t, J = 3.5 Hz, 1 H), 6.79 (d, J = 8.5 Hz, 1 H), 7.04 (ddd, J = 8.5, 2.0, 0.5 Hz, 1 H), 7.34 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.18 (q'), 65.48 (t'), 70.41 (t'), 101.93 (d'), 112.03 (s'), 113.62 (d'), 128.23 (d'), 132.12 (s'), 133.79 (d'), 153.04 (s'); exact mass *m/z* calcd for $C_{11}H_{13}{}^{79}BrO_3$ 272.0048, found 272.0048. Anal. Calcd for $C_{11}H_{13}BrO_3$ C, 48.37; H, 4.80; Br, 29.26. Found: C, 48.37; H, 4.74; Br, 29.37.

General Procedure (A) for Radical Reduction of Aryl Bromides. The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser that was sealed with a rubber septum. The system was flushed with Ar for 5–10 min, and a solution of the reducing agent [Ph_3SnD[110] or Bu_3SnD (Aldrich)] in dry PhH, using the indicated amount of solvent to transfer the stannane, was injected. The mixture was heated at 80 °C, and a solution of AIBN in dry PhH was injected by syringe pump over 1–2.5 h. Refluxing was continued for an arbitrary period of 0–20 h after the addition. The reaction mixture was cooled, and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

Reduction of [2-Bromo-4-methylphenyloxy)methyl]-1,3-dioxolane (243).

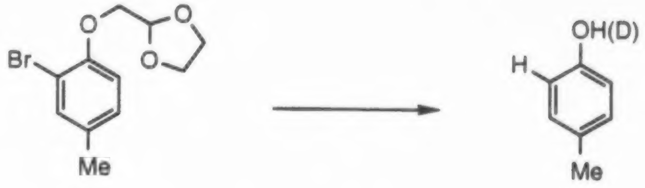


243 **243r**

The general procedure (A) for radical reduction of aryl bromides was followed, using bromide **243** (84.3 mg, 0.31 mmol), Ph_3SnD (282 mg, 0.80 mmol) in dry PhH (7 mL), and a solution of AIBN (25 mg, 0.15 mmol) in dry PhH (1 mL) added over 2 h, at which point the mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:9 Et_2O–hexane, gave reduced compound **243r** (51.6 mg, 85%) as an impure [^1H NMR (300 MHz)], oil. The contaminant (*ca.* 20%) is probably *p*-cresol. Compound **243r** had: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3 H), 3.93–4.09 (m, 6 H), 5.28 (t, J = 4.0 Hz, *ca.* 0.9 H), 6.83 (d, J = 9.0 Hz, *ca.* 1.1 H), 7.05–7.11 (m, 2 H); ^2H NMR ($CHCl_3$, 61.423 MHz) δ 4.00 (br s, < 0.01 ^2H), 5.14 (s, 0.06 ^2H), 6.89 (s, 0.93 ^2H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.49 (q'), 65.31 (t'), 68.99 (t'), 102.11 (d'), 114.58 (d'), 129.81 (d'), 129.91 (d'), 130.45 (s'), 156.48 (s'); exact mass *m/z* calcd for $C_{11}H_{13}DO_3$ 195.1006, found 195.1002.

General Procedure (B) for Radical Reduction of Aryl Bromide. The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser that was sealed with a rubber septum. The system was flushed with Ar for 5-10 min, and dry PhH was injected. The solution was refluxed, and separate solutions of Ph_3SnD or Bu_3SnD (Aldrich) and AIBN in PhH were injected simultaneously by syringe pump over 5 h. Refluxing was continued for an arbitrary period of 10 h after the addition. The reaction mixture was cooled, and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

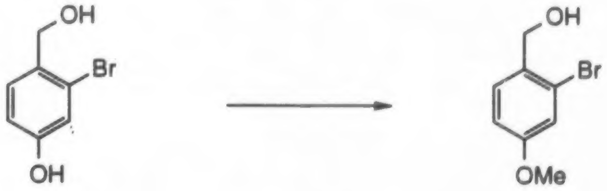
4-Methylphenol (*p*-cresol) (256).



243 **256**

The general procedure (B) for radical reduction of aryl bromides was followed, using bromide **243** (54 mg, 0.20 mmol) in PhH (10 mL), Ph_3SnD (71 mg, 0.20 mmol) in dry PhH (2.5 mL) and AIBN (17 mg, 0.1 mmol) in PhH (2.5 mL), with addition over 5 h, and a reflux period of 10 h after the addition. After workup, flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:19 acetone–hexane, gave impure [^1H NMR] *p*-cresol **256** (*ca.* 10 mg, 27%).

2-Bromo-4-methoxybenzyl alcohol (242).

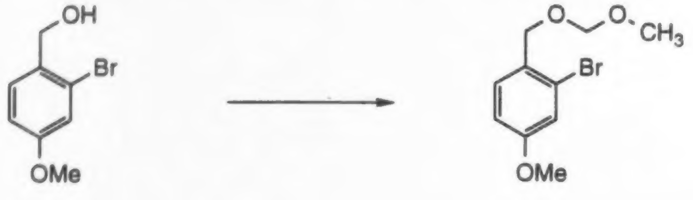


419 **242**

Anhydrous K_2CO_3 (3.00 g, 22 mmol) was added to a stirred solution of phenol[193] **419** (1.35 g, 6.65 mmol) and MeI (2.30 g, 16 mmol) in acetone (reagent grade, 25 mL). Stirring was maintained at room temperature overnight. Water (200 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 × 25 cm), using 1:4 acetone–hexane, gave alcohol **242** (1.191 g, 83%) as a pure [^1H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 3357, 1605, 1492, 1238, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (br s, 1 H), 3.77 (s, 3 H), 4.65 (s, 2 H), 6.82 (dd, J =

8.5, 2.5 Hz, 1 H), 7.07 (d, *J* = 2.5 Hz, 1 H), 7.31 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 55.60 (t'), 64.73 (q'), 113.42 (d'), 118.17 (d'), 123.34 (s'), 130.10 (d'), 131.95 (s'); exact mass *m/z* calcd for $C_8H_9{}^{79}BrO_2$ 215.9786, found 215.9790. Anal. Calcd for $C_8H_9BrO_2$ C, 44.27; H, 4.18; Br, 36.81. Found: C, 44.42; H, 4.12; Br, 36.69.

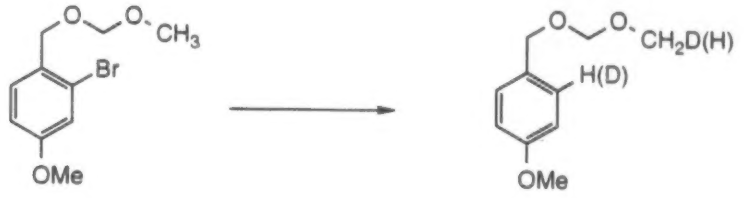
2-Bromo-4-methoxy-1-(methoxymethoxymethyl)benzene (244).



242 **244**

NaH (60% dispersion in mineral oil, 120 mg, 3.0 mmol) was added to a stirred solution of bromide **242** (418 mg, 1.92 mmol) and CH_3OCH_2Cl (0.25 g, 3.1 mmol) in dry THF (20 mL). Stirring was continued at room temperature for 4 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 1:9 Et_2O–hexane, gave bromide **244** (435.3 mg, 86%) as a pure [^1H NMR (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2941, 1605, 1495, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.55 (s, 3 H), 3.80 s, 3 H), 4.63 (s, 2 H), 4.75 (s, 2 H), 6.87 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.04 (d, *J* = 2.5 Hz, 1 H), 7.38 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 55.58 (q'), 68.57 (t'), 95.98 (t'), 113.39 (d'), 118.09 (d'), 123.90 (s'), 129.30 (s'), 130.66 (d'), 159.72 (s'); exact mass *m/z* calcd for $C_{10}H_{13}{}^{79}BrO_3$ 260.0048, found 260.0051. Anal. Calcd for $C_{10}H_{13}BrO_3$ C, 45.00; H, 5.02. Found: C, 44.96; H, 4.93.

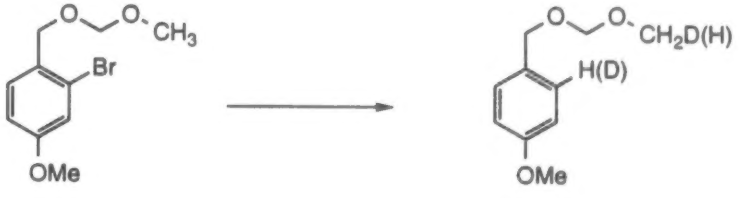
Reduction of 2-Bromo-4-methoxy-1-(methoxymethoxymethyl)benzene (244).



244 **244r**

General procedure (A) for radical reduction of aryl bromides was followed, using bromide **244** (82.2 mg, 0.316 mmol), Ph_3SnD (221.6 mg, 0.63 mmol) in dry PhH (5.3 mL), and a solution of AIBN (20 mg, 0.12 mmol) in dry PhH (1 mL) was added over over 2.5 h, at which point the mixture was evaporated. Flash chromatography of the residue over silica gel (1.8 × 13 cm), using increasing amounts of Et_2O in hexane (from 5% to 10%), gave reduced compound **244r** (47.5 mg, 82%) as a colorless oil: FTIR ($CHCl_3$ cast) 2945, 1608, 1499, 1236, 1149, 1102, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.41 (s, 2.9 H), 3.71 (s, 3 H), 4.54 (s, 2 H), 4.69 (s, 2 H)6.87–6.92 (m, 2 H), 7.27–7.32 (m, 1.1 H); ^{2}H NMR ($CHCl_3$, 61.423) δ 3.43 (s, 0.03 ^{2}H), 7.34 (s, 0.97 ^{1}H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 55.32 (q'), 68.84 (t'), 95.48 (t'), 113.80 (d'), 113.90 (d'), 129.58 (d'), 129.91 (s'), 159.33 (s').

Reduction of 2-Bromo-4-methoxy-1-(methoxymethoxymethyl)benzene (244).



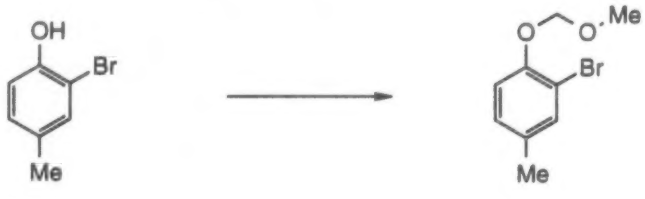
244 **244r**

General procedure (B) for radical reduction of aryl bromides was followed, using bromide **244** (52 mg, 0.20 mmol) in PhH (10 mL), Ph_3SnD, (72 mg, 0.20 mmol) in dry

PhH (2.5 mL), and AIBN (5 mg, 0.03 mmol) in PhH (2.5 mL), with addition over 5 h. Refluxing was continued for 10 h after the addition. After work up, flash chromatography of the residue over silica gel (1.8 × 12 cm), using increasing amounts of Et_2O in hexane (from 3% to 10%), gave reduced compound **244r** (25.1 mg, 69%) as a colorless oil: ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.33–3.42 (m, 2.35 H), 3.78 (s, 3 H), 4.50 (s, 1.95 H), 4.66 (s, 2 H), 7.83–6.92 (m, 2 H), 7.22–7.32 (m, 1.70 H); exact mass *m/z* calcd for $C_{10}H_{13}DO_3$ 183.1006, found 183.0999.

Note: The multiplet at δ 3.33–3.42 indicated the presence of CH_2D.

2-Bromo-4-methyl-1-(methoxymethoxy)benzene (245).

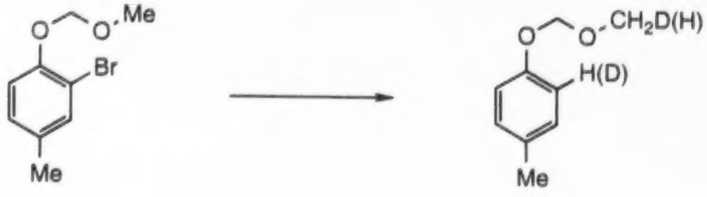


241 **245**

Sodium hydride (60% dispersion in mineral oil, 0.40 g, 10 mmol) was added to a stirred solution of phenol[115] **241** (935 mg, 5.00 mmol) and CH_3OCH_2Cl (1.27 g, 15.8 mmol) in dry THF (25 mL). Stirring was continued at room temperature overnight. Water (50 mL) was added, and the mixture was extracted with $CHCl_3$ (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (20 × 2.8 cm), using 1:9 Et_2O–hexane, gave bromide **245** (1.066 g, 92%) as a pure [^1H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 1494, 1243, 1084, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3 H), 3.52 (s, 3 H), 5.22 (s, 2 H), 7.02–706 (m, 2 H), 7.48 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.26 (q'), 56.34 (q'), 95.39 (t'), 112.72 (s'), 116.39 (d'), 128.96 (d'), 133.05 (s'), 133.73 (d'), 151.60 (s'); exact mass *m/z* calcd for $C_8H_8{}^{79}BrO$ (M - OMe)$^+$ 198.9759, found 198.9757. CIMS, *m/z* calcd for $C_9H_{11}{}^{79}BrO_2$ 230, found 230, calc for $C_9H_{15}{}^{79}BrNO_2$

(M plus NH_4)$^+$ 248, found 248. Anal. Calcd for $C_9H_{11}BrO_2$ C, 46.78; H, 4.80; Br, 34.58. Found: C, 46.90; H, 4.90; Br, 34.21.

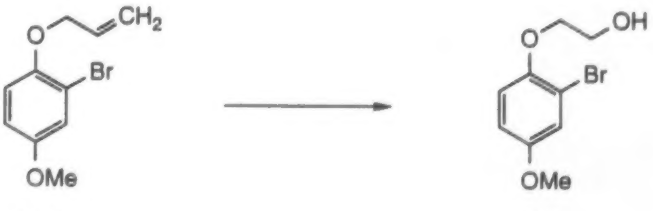
Reduction of 2-bromo-4-methyl-1-(methoxymethoxy)benzene (245).



245 **245r**

General procedure (A) for radical reduction of aryl bromide was followed, using bromide **245** (69.3 mg, 0.30 mmol), Ph_3SnD (126 mg, 0.36 mmol) in dry PhH (24 mL), and AIBN (8 mg, 0.05 mmol) in dry PhH (1 mL), which was added all at once. Refluxing was continued for 20 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 × 14 cm), using increasing amounts of Et_2O in hexane (2% to 10%), gave a complicated mixture of compounds. The ^1H NMR (300 MHz) spectrum indicated starting material (*ca.* 66%), and some reduced compound **245r** (*ca.* 33 %), and contamination by stannane residues. The ratio of direct reduction–hydrogen abstraction was approximately 3:2 in the best experiment.

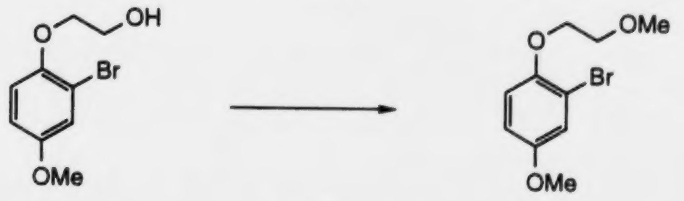
2-(2-Bromo-4-methylphenyloxy)ethanol (420).



417 **420**

An ozone-oxygen stream was bubbled through a stirred and cooled (-78 °C) solution of **417** (1.14 g, 5.02 mmol) in a 1:4 mixture of CH_2Cl_2–MeOH (100 mL) until the solution turned faintly purple (15 min). The mixture was stirred for 5 min (persistence of the purple color), and $NaBH_4$ (0.96 g, 25.4 mmol) was added.[195] Stirring was maintained at -78 °C for 30 min, the cooling bath was removed, and stirring was continued at room temperature overnight under argon. Water (300 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.7 × 20 cm), using increasing amounts of EtOAc in hexane (from 15% to 20%), gave alcohol **420** (1.059 g, 91%) as a homogeneous [^{1}H NMR (300 MHz)], white solid: mp 51–52 °C; FTIR ($CHCl_3$ cast) 3377, 2925, 1496, 1253, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (br s, 1 H), 2.28 (s, 3 H), 3.93–3.98 (m, 2 H), 4.08–4.13 (m, 2 H), 26.82 (d, *J* = 8.0 Hz, 1 H), 7.05 (ddd, *J* = 8.0, 2.0, 0.5 Hz, 1 H), 7.34–7.38 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.26 (q'), 61.41 (t') ,71.18 (t'), 112.45 (s'), 114.25 (d'), 129.04 (d'), 132.46 (s'), 133.79 (d'), 152.90 (s'); exact mass *m/z* calcd for $C_7H_7{}^{79}BrO$ (M - C_2H_4O)$^+$ 185.9684, found 185.9682; CIMS, *m/z* calcd for $C_9H_{11}BrO_2$ 230, found 230, calcd for $C_9H_{15}BrNO_2$ (M + NH_4)$^+$ 248, found 248. Anal. Calcd for $C_9H_{11}BrO_2$ C, 46.78; H, 4.80; Br, 34.58. Found: C, 46.80; H, 4.48; Br, 34.60.

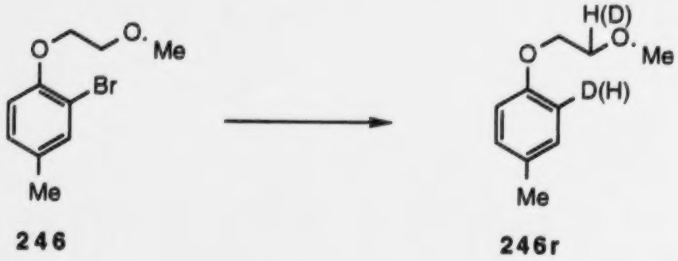
2-Bromo-4-methyl-1-(2-methoxyethoxy)benzene (246).



420 **246**

NaH (60% dispersion in oil, 0.20 g, 5.0 mmol) was added to a stirred solution of alcohol **420** (574.4 mg, 2.49 mmol) and MeI (1.05 g, 7.40 mmol) in dry THF (25 mL). The flask was equipped with a condenser, and stirring was continued at room temperature overnight. Water (100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated, and flash chromatography of the residue over silica gel (20 × 2.8 cm), using 1:19 EtOAc–hexane, gave bromide **246** (556 mg, 91%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2925, 1496, 1284, 1253, 1129, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3 H), 3.47 (s, 3 H), 3.76–3.81 (m, 2 H), 4.10–4.16 (m, 2 H), 6.82 (d, J = 8.5 Hz, 1 H), 7.02–7.07 m, 1 H), 7.34–7.37 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.22 (q'), 59.50 (q'), 69.31 (t'), 71.01 (t'), 112.34 (s'), 114.08 (d'), 128.88 (d'), 132.05 (s'), 133.83 (d'), 153.29 (s'); exact mass *m/z* calcd for $C_{10}H_{13}{}^{79}BrO_2$ 244.0099, found 244.0099. Anal. Calcd for $C_{10}H_{13}BrO_2$ C, 49.00; H, 5.35; Br, 32.60. Found: C, 49.31; H, 5.38; Br, 32.23.

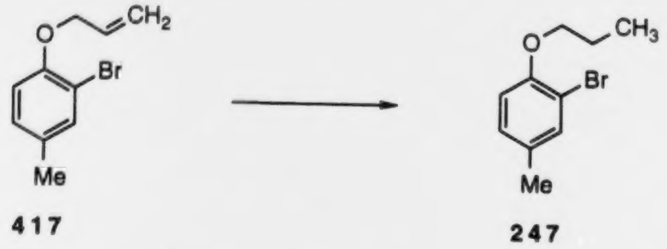
Reduction of 2-bromo-4-methyl-1-(2-methoxyethoxy)benzene (246).



General procedure (A) for radical reduction of aryl bromides was followed, using bromide **246** (86.4 mg, 0.35 mmol), Ph_3SnD (248.2 mg, 0.71 mmol) in dry PhH (6 mL), and slow addition of a solution of AIBN (20 mg, 0.12 mmol) in dry PhH (1 mL) over 2 h, at which stage the solvent was evaporated. Flash chromatography of the residue over silica gel (1.8 × 1.5 cm), using 7:93 Et_2O–hexane, gave reduced compound **246r** (40.1, 68%) as an oil, which contains impurities [*ca.* 5% (^{1}H NMR)]: FTIR ($CDCl_3$ cast) 2924, 1510, 1493, 1244, 1128 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3 H), 3.46 (s, 3 H), 3.70–3.77 (m, 1.63 H), 4.04–4.11 (m, 2 H), 6.78–6.85 (m, 1.37 H), 7.027.10 (m, 2 H); ^{2}H NMR ($CHCl_3$, 61.24 MHz) δ 3.47 (s, 0.05 ^{2}H), 3,75 (s, 0.26 ^{2}H), 6.88 (s, 0.69 ^{2}H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.49 (q'), 59.23 (q'), 67.40 (t'), 71.19 (t'), 114.57 (d'), 129.79 (d'), 129.90 (d'), 130.15 (s'), 156.69 (s'), 156.73 (s'), also a triplet at δ

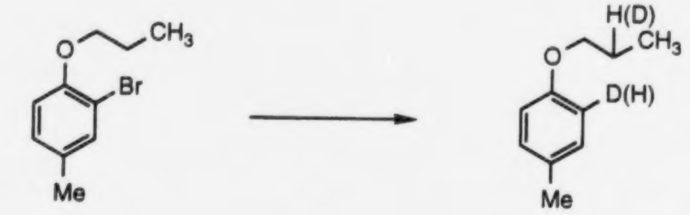
70.82 (d', J_{CD} = 22 Hz) for the CHD signal; exact mass *m/z* calcd for $C_{10}H_{13}DO_2$ 167.1057, found 167.1056.

2-Bromo-4-methyl-1-propyloxybenzene (247).



H_2 gas (balloon, *ca.* 2 L) was bubbled through a stirred mixture of allyl ether **417** (420 mg, 1.85 mmol) and 5% Pd/C (100 mg) in hexane (100 mL).[196] Stirring was continued under a H_2 atmosphere for 8 h. The mixture was filtered through a pad of Celite (2 × 3 cm), the pad was washed with Et_2O (3 × 50 mL), and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (15 × 1.8 cm), using 1:49 Et_2O–hexane, gave bromide **247** (369 mg, 87%) as a colorless oil: FTIR ($CHCl_3$ cast) 2965, 1497, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (t, J = 7.0 Hz, 3 H), 1.76–1.88 (m, 2 H), 2.24 (s, 3 H), 3.93 (t, J = 7.0 Hz, 2 H), 6.75 (d, J = 8.0 Hz, 1 H), 7.00 (ddd, J = 8.0, 2.5, 0.5 Hz, 1 H), 7.34 (dd, J = 2.5, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 10.69 (q'), 20.20 (q'), 22.62 (t'), 70.94 (t'), 112.11 (s'), 113.42 (d'), 128.81 (d'), 131.36 (s'), 133.75 (d'), 153.41 (s'); exact mass *m/z* calcd for $C_{10}H_{13}{}^{79}BrO$ 228.0150, found 228.0155. Anal. Calcd for $C_{10}H_{13}BrO$ C, 52.42; H, 5.72; Br, 34.87. Found: C, 52.57; H, 5.85; Br, 34.56.

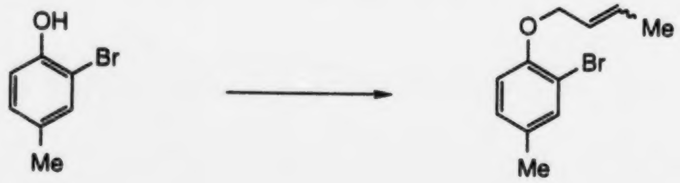
Reduction of 2-bromo-4-methyl-1-propyloxybenzene (247).



247 **247r**

General procedure (A) for radical reduction of aryl bromides was followed, using bromide **247** (77 mg, 0.37 mmol), Ph_3SnD (236 mg, 0.67 mmol) in dry PhH (5.7 mL), and slow addition of a solution of AIBN (20 mg, 0.12 mmol) in dry PhH (1 mL) over 1.5 h, at which point the solvent was evaporated. Flash chromatography of the residue over silica gel (1.8 × 16 cm), using 1:19 $CHCl_3$–hexane, gave reduced compound **247r** (25.1, 49%) as a colorless oil, which contains impurities [*ca.* 5% (^{1}H NMR)]: FTIR ($CHCl_3$ cast) 2964, 1511, 1494, 1242, cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, J = 7.5 Hz, 3 H), 1.73–1.87 (m, 1.88 H), 2.28 (s, 3 H), 3.91 (t, J = 7.5 Hz, 2 H), 6.78–6.85 (m, 1.22 H), 7.05–7.11 (m, 2 H); ^{2}H NMR ($CHCl_3$, 61.24 MHz) δ 1.79 (s, 0.13 ^{2}H), 6.85 (s, 0.87 ^{2}H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 10.56 (q'), 20.48 (q'), 22.68 (t'), 69.64 (t'), 114.45 (d'),129.68 (s'), 129.76 (d'), 129.87 (d'), 157.02 (s').

2-Bromo-1-(2-butenoxy)-4-methylbenzene (421).

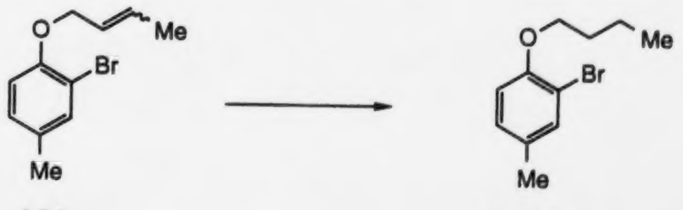


241 **421**

NaH (60% dispersion in oil, 0.30 g, 7.5 mmol) was added to a stirred solution of phenol[115] **241** (935 mg, 5.00 mmol) and crotyl bromide (tech, 1.9 g, 14 mmol) in dry THF. The flask was equipped with a condenser, and stirring was continued at room temperature overnight. At that time,the reaction was not complete [TLC control, silica, Et_2O–hexane (1:9)]. The mixture was then heated at 65 °C for 12 h. The reaction was cooled to room temperature, water (200 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 19 cm), using 1:19 $CHCl_3$–hexane, gave bromide **421** (1.152 g, 95.5%) as a colorless oil. The product was a mixture of geometric isomers [^1H NMR (300 MHz)]: FTIR ($CHCl_3$ cast) 2919, 1495, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.72–1.78 (m, 3 H), 2.26 (s, 3 H), 4.48–4.52 (m, 1.70 H), 4.63–4.67 (m, 0.30 H), 5.67–5.79 (m, 1.15 H), 5.81–5.99 (m, 0.85 H), 6.77–6.83 (m, 1 H), 7.00–7.05 (m, 1 H), 7.34–7.37 (m 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 17.87 and 20.19 (2 q'), 65.37* (t'), 70.04 (t'), 112.16* (s'), 113.89 (d'), 125.53 (d'), 128.53 (d'), 130.26 (d'), 131.96 (s'), 133.78 (d'), 153.04 (s'); exact mass *m/z* calcd for $C_{11}H_{13}{}^{79}BrO$ 240.0149, found 240.0149. Anal. Calcd for $C_{11}H_{13}BrO$ C, 54.79; H, 5.43; Br, 33.14. Found: C, 54.90; H, 5.42; Br, 33.23.

* Corresponds to the minor isomer.

2-Bromo-1-butyloxy-4-methylbenzene (248).

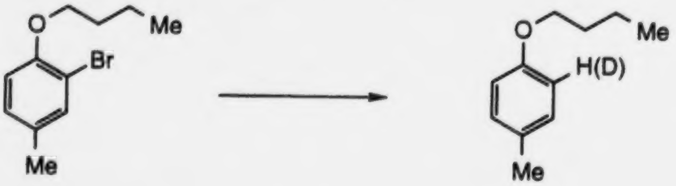


421 **248**

H_2 gas (balloon, *ca.* 2 L) was bubbled through a stirred mixture of allyl ether **421** (500 mg, 2.07 mmol) and 5% Pd/C (100 mg) in hexane (50 mL).[196] Stirring was continued for 6 h, under a H_2 atmosphere . The mixture was filtered through a pad of Celite (2 × 3 cm), the pad was washed with Et_2O (4 × 50 mL), and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1.8 × 17 cm), using 1:19

$CHCl_3$–hexane, gave bromide **248** (448 mg, 89%) as a pure [^{1}H NMR (300 MHz)], colorless oil : FTIR ($CHCl_3$ cast) 2958, 2933, 1497, 1285, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J = 7.0 Hz, 3 H), 1.46–1.60 (m, 2 H), 1.76–1.86 (m, 2 H), 2.25 (s, 3 H), 3.99 (t, J = 6.5 Hz, 2 H), 6.78 (d, J = 8.0 Hz, 1 H), 7.04 (ddd, J = 8.0, 2.0, 0.5 Hz, 1 H), 7.34–7.37 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 13.88 (q'), 19.28 (t'), 20.18 (q'), 31.29 (t'), 69.14 (t'), 112.07 (s'), 113.36 (d'), 128.79 (d'), 131.33 (s'), 133.73 (d'), 153.42 (s'); exact mass *m/z* calcd for $C_{11}H_{15}{}^{79}BrO$ 242.0307, found 242.0306. Anal. Calcd for $C_{11}H_{15}BrO$ C, 54.34; H, 6.22; Br, 32.86. Found: C, 54.37; H, 6.23; Br, 33.01.

Reduction of 2-bromo-1-butyloxy-4-methylbenzene (248).

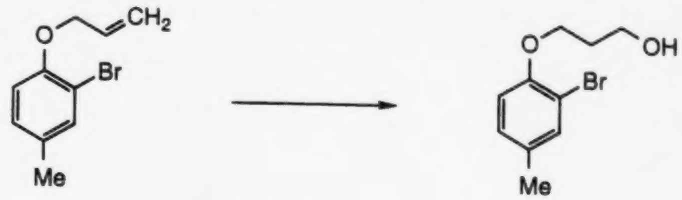


248 **248r**

General procedure (A) for radical reduction of aryl bromides was followed, using bromide **248** (84.2 mg, 0.346 mmol), Ph_3SnD (243 mg, 0.69 mmol) in dry PhH (6 mL), and AIBN (16 mg, 0.1 mmol) in dry PhH (1 mL), with addition over 2 h. Refluxing was continued for 2 h. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using increasing amounts of Et_2O in hexane (from 0% to 3%), gave impure **248r** (*ca.* 50%) as a a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, J = 7.5 Hz, 3 H), 1.43–1.57 (m, 1.87 H), 1.71–1.82 (m, 1.87 H), 4.93 (t, J = 6.5 Hz, 2 H), 6.78–6.86 (m, 1.28 H), 7.04–7.11 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 13.88 (q'), 19.31 (t'), 20.48 (q'), 31.45 (t'), 67.79 (t'), 114.43 (d'), 129.67 (s'), 129.76 (d'), 129.87 (d'), 157.09 (s'). A similar reaction, but at four times the dilution, had: ^{1}H NMR ($CDCl_3$, 300 MHz) δ

0.99 (t, *J* = 3 H), 1.44–1.53 (m, 1.58 H), 1.70–1.82 (m, 1.62 H), 2.28 (s, 3 H), 3.95 (t, *J* = 6.5 Hz, 2 H), 6.79–7.84 (m, 1.81 H), 7.06–7.12 (m, 2 H).

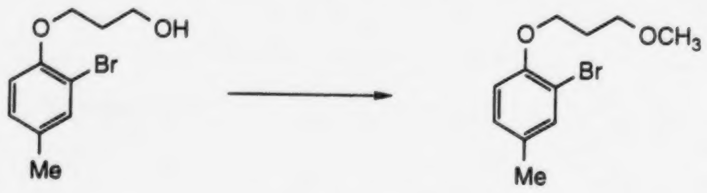
3-(2-Bromo-4-methyl-1-phenyloxy)propanol (422).



417 **422**

A solution of **417** (2.231 g, 9.82 mmol) in dry THF (5.0 ml plus 2 × 2.5 mL as a rinse) was added to a stirred solution of 9-BBN-H dimer[197] (1.387 g, 2.57 mmol) in dry THF (100 mL). The round-bottomed flask was lowered in a preheated (65 °C) oil bath, and the mixture was heated for 1.5 h. The solution was cooled to room temperature, then 98% EtOH (3.0 mL), 2.0 N aqueous NaOH (2 N, 3.0 mL), and 30% H_2O_2 (2.0 mL) were added carefully, in this order. The mixture was then heated at 50 °C for 1 h. The mixture was cooled to room temperature, and water (200 mL) was added. The mixture was acidified with 2 N aqueous HCl (5.0 mL), and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 3:7 EtOAc–hexane, gave alcohol **422** (2.39 g, 99%) as a pure [^{1}H NMR (300 MHz)], white solid: mp 35–37 °C; FTIR (CH_2Cl_2 cast) 3340, 1497, 1254, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.09 (p, *J* = 5.5 Hz, 2 H), 2.18 (s, 3 H), 3.91 (t, *J* = 5.5 Hz, 2 H), 4.16 (t, *J* = 5.5 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 7.06 (ddd, *J* = 8.5, 2.0, 0.5 Hz, 1 H), 7.35 (dd, *J* = 2.0, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.19 (q'), 31.83 (t'), 61.00 (t'), 67.89 (t'), 111.81 (s'), 113.00 (d'), 128.92 (d'), 131.85 (s'), 133.66 (d'), 152.93 (s'); exact mass *m/z* calcd for $C_{10}H_{13}{}^{79}BrO_2$ 277.0098, found 244.0090. Anal. Calcd for $C_{10}H_{13}BrO_2$ C, 49.00; H, 5.35; Br, 32.60. Found: C, 49.01; H, 5.41; Br, 32.72.

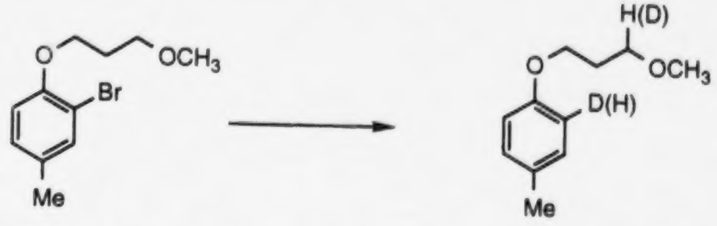
2-Bromo-1-(3-methoxy-1-propyloxy)-4-methylbenzene (249).



422 **249**

NaH (60% dispersion in oil, 0.24 g, 6.0 mmol) was added to a stirred solution of alcohol **422** (735 mg, 3.00 mmol) and MeI (1.28 g, 9.0 mmol) in dry THF (20 mL). The flask was equipped with a condenser, and stirring was continued at room temperature overnight. Water (100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 1:19 EtOAc–hexane, gave bromide **249** (726.2 mg, 93%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 2924, 2875, 1497, 1469, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06 (pentet, J = 6.0 Hz, 2 H), 2.25 (s, 3 H), 3.34 (s, 3 H), 3.58 (t, J = 6.0 Hz, 2 H), 4.07 (t, J = 6.0 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 1 H), 7.02 (ddd, J = 8.5, 2.0, 0.5 Hz, 1 H), 7.33 (dd, J = 2.0, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.20 (q'), 29.62 (t'), 58.78 (t'), 66.19 (t'), 69.17 (t'), 112.04 (s'), 113.44 (d'), 128.85 (d'), 131.51 (s'), 133.71 (d'), 153.26 (s'); exact mass *m/z* calcd for $C_{11}H_{15}{}^{79}BrO_2$ 258.0255, found 258.0257. Anal. Calcd for $C_{11}H_{15}BrO_2$ C, 50.98; H, 5.83; Br, 30.83. Found: C, 51.22; H, 6.02; Br, 31.02.

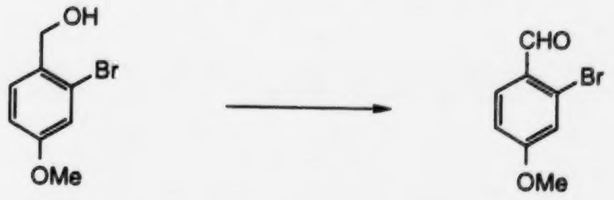
Reduction of 2-bromo-1-(3-methoxy-1-propyloxy)-4-methylbenzene (249).



249 **249r**

General procedure (A) for radical reduction of aryl bromides was followed, using bromide **249** (103.8 mg, 0.40 mmol), Ph_3SnD (282 mg, 0.80 mmol) in dry PhH (7 mL), and AIBN (20 mg, 0.12 mmol) in dry PhH (1.0 mL), with addition over 2 h. Refluxing was continued for 2 h. Flash chromatography of the residue over silica gel (12 × 1.8 cm), using 1:19 Et_2O–hexane, gave reduced compound **249r** (68.8 mg, 94%) as an oil: FTIR ($CHCl_3$ cast) 2926, 2874, 1512, 1494, 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.04 (p, J = 6.0 Hz, 2 H), 2.28 (s, 3 H), 3.36 (s, 3 H), 3.57 (t, J = 6.0 Hz, 1.68 H), 4.05 (t, J = 6.0 Hz, 2 H), 6.79–6.84 (m, 1.32 H), 7.05–7.11 (m, 2 H); ^2H NMR ($CHCl_3$, 61.24 MHz) δ 3.55 (s, 0.31 ^2H), 6.84 (s, 0.69 ^2H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.48 (q), 29.75 (t), 58.73 (q), 64.94 (t), 69.39 (t), 114.45 (d), 129.28 (d), 129.88 (s), 156.89 (s); exact mass m/z calcd for $C_{11}H_{15}DO_2$ 181.1214, found 181.1214.

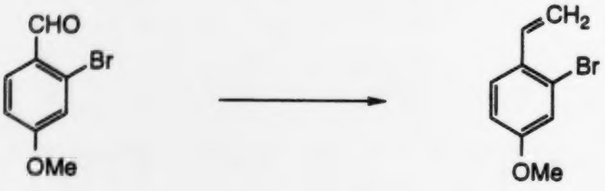
2-Bromo-4-methoxybenzaldehyde (423).



242 **423**

Activated MnO_2[198] (2.87 g, 33.0 mmol) was added to a stirred solution of alcohol **242** (717 mg, 3.30 mmol) in pentane (50 mL). The flask was equipped with a condenser, and stirring was continued overnight with exposure to the air. The mixture was filtered through Celite (3.5 × 2.5 cm), the pad was washed with Et_2O (4 × 50 mL), and the filtrate was evaporated to give aldehyde **423** as an solid which was suitable for the next step. Flash chromatography of the residue from an similar experiment over silica gel, gave aldehyde **423** (70% yield) as a white solid, and had: mp 75–76 °C; FTIR ($CHCl_3$ cast) 1673, 1598, 1252, 815 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 2.90 (s, 3 H), 6.34 (ddd, J = 0.5, 2.5, 8.5 Hz, 1 H), 6.75 (d, J = 2.5 Hz, 1 H), 7.79 (d, J = 8.5 Hz, 1 H), 10.25 (d, J = 0.5 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.469 MHz) δ 55.02 (q'), 114.30 (d'), 118.42 (d'), 128 (s') [obscured by C_6D_6 signal], 128.59 (s'), 131.39 (d'), 164.36 (s'), 189.27 (d'); exact mass *m/z* calcd for $C_8H_7{}^{79}BrO$ 213.9630, found 213.9624. Anal. Calcd for C_8H_7BrO C, 44.68; H, 3.28; Br, 37.16. Found: C, 44.55; H, 2.95; Br, 37.48.

2-Bromo-4-methoxystyrene (424).

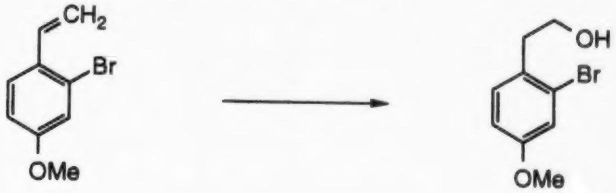


423 **424**

$Ph_3PCH_3Br^{199}$ (2.36 g, 6.61 mmol) was tipped into a stirred suspension of *t*-BuOK (0.56 g, 97 %, 5.0 mmol) in dry THF (30 mL). Stirring was continued for 5 min, and a solution of crude aldehyde **423** (3.30 mmol, assuming complete conversion) in dry THF (5.0 mL plus 2 × 2.5 mL as rinse) was added. Stirring was maintained at room temperature for 2 h. Water (150 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.8 × 18 cm), using 1:49 Et_2O–hexane, gave bromide **424** (584.4 g, 83%, over two steps) as a pure [^1H NMR (300 MHz)], colorless oil oil: FTIR ($CDCl_3$ cast) 1601, 1486, 1287, 1241, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.80 (s, 3 H), 5.25 (dd, J = 11.0, 1.0 Hz, 1 H), 5.58 (dd, J =

17.5, 1.0 Hz, 1 H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.99 (dd, *J* = 17.5, 11 Hz, 1 H), 7.10 (d, *J* = 2.5 Hz, 1 H), 7.49 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 55.60 (q'), 114.18 (d'), 114.46 (t'), 117.60 (d'), 124.01 (s'), 127.26 (d'), 130.12 (s'), 135.15 (d'), 159.66 (s'); exact mass *m/z* calcd for $C_9H_9{}^{81}BrO$ 213.9630, found 213.9625.

2-Bromo-4-methoxyphenethyl alcohol (425).

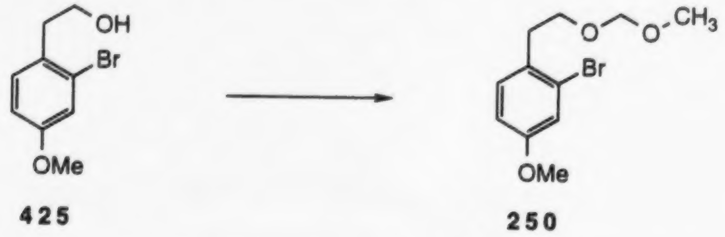


424 **425**

A solution of bromide **424** (560 mg, 2.63 mmol) in dry THF (2 ml plus 2 × 1 mL as a rinse) was added to a stirred solution of 9-BBN-H dimer[197] (0.70 g, 5.74 mmol) in dry THF (46 mL). The round-bottomed flask was lowered into a preheated (65 °C) oil bath, and the mixture was heated for 1.5 h. The solution was cooled to room temperature, then 98% EtOH (1.8 mL), 2.0 N aqueous NaOH (2 N, 1.8 mL), and 30% H_2O_2 (1.2 mL) were added carefully, in that order. The mixture was then heated at 50 °C for 1 h. The mixture was cooled to room temperature, and water (150 mL) was added. The mixture was acidified with 2 N aqueous HCl (*ca.* 3 mL), and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 17 cm), using 3:7 EtOAc–hexane, gave alcohol **425** (328.6 g, 54%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 3360, 2931, 1605, 1493, 1240, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (br s, 1 H), 2.94 (t, *J* = 7.0 Hz, 2 H), 3.75 (s, 3 H), 3.82 (t, *J* = 7.0 Hz, 2 H), 6.80 (dd, *J* = 8.2, 2.5 Hz, 1 H), 7.10 (d, *J* = 2.5 Hz, 1 H), 7.15 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 38.46 (t'), 55.59 (q'), 62.39 (t'), 113.68 (d'), 118.25

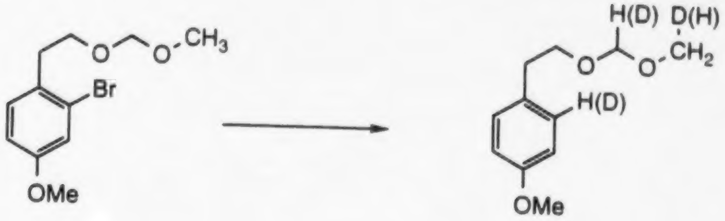
(d'), 124.80 (s'), 129.71 (s'), 131.58 (d'), 158.90 (s'); exact mass *m/z* calcd for $C_8H_8{}^{79}BrO$ (M - OMe)$^+$ 198.9758, found 198.9757.

2-Bromo-4-methoxy-1-(2-methoxymethoxyethyl)benzene (250).



NaH (60% dispersion in mineral oil, 75 mg, 1.88 mmol) was added to a stirred solution of bromide **425** (220 mg, 0.95 mmol) and $MeOCH_2Cl$[194] (0.23 g, 2.8 mmol) in dry THF (20 mL). Stirring was continued at room temperature overnight. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 13 cm), using 1:19 Et_2O–hexane, gave bromide **250** (137.3 g, 52%) as a pure [^1H NMR (300 MHz)], oil: FTIR ($CHCl_3$ cast) 3425, 2966, 1721, 1036, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.98 (t, J = 7.0 Hz, 2 H), 3.31 (s, 3 H), 3.73 (t, J = 7.0 Hz, 2 H), 3.78 (s, 3 H); 4.62 (s, 2 H), 6.81 (dd, J = 8.5, 2.5 Hz, 1 H), 7.10 (d, J = 2.5 Hz, 1 H), 7.29 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.60 (t'), 55.19 (q'), 55.54 (q'), 66.98 (t'), 96.38 (t'), 113.59 (d'), 117.96 (d'), 124.07 (s'), 130.06 (s'), 131.39 (d'), 158.73 (s'); exact mass *m/z* calcd for $C_{11}H_{15}{}^{79}BrO_3$ 274.0204, found 274.0205. Anal. Calcd for $C_{11}H_{15}BrO_3$ C, 45.00; H, 5.02. Found: C, 44.96; H, 4.93.

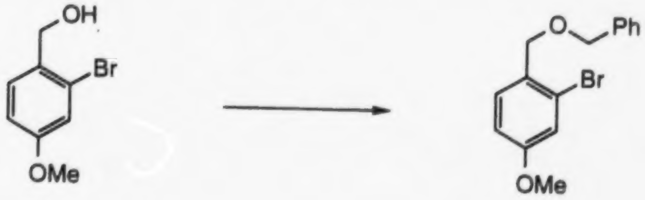
Reduction of 2-bromo-4-methoxy-1-(2-methomethoxyethyl)benzene (250).



250 **250r**

General procedure (A) for radical reduction of aryl bromides was followed, using bromide **250** (55 mg, 0.20 mmol), Ph_3SnD (84 mg, 0.24 mmol) in dry PhH (16 mL), and AIBN (8 mg, 0.05 mmol) in dry PhH (2 mL plus 2 mL as a rinse), with no slow addition. Stirring was continued at 80 °C overnight. Flash chromatography of the residue over silica gel (1.8 × 11 cm), using 1:19 Et_2O–hexanes, gave an inseparable mixture [^1H NMR (300 MHz)]. The ratio starting material–reduced compound was 1:1.6. The approximate ratio of direct reduction–abstraction was estimated from the complex ^1H NMR, and reported in Discussion, Table 1.

1-(Benzyloxymethyl)-2-bromo-4-methoxybenzene (251).

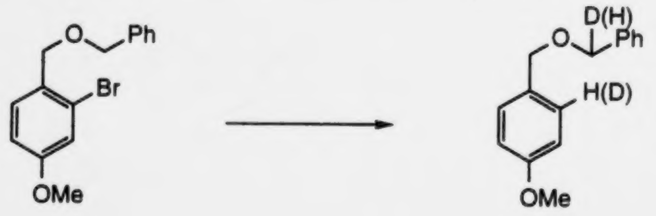


242 **251**

NaH (60% dispersion in oil, 40 mg, 72.0 mmol) was added to a stirred solution of alcohol **242** (217 mg, 1.0 mmol) and benzyl bromide (0.34 g, 2.0 mmol) in dry THF (20 mL). The flask was equipped with a condenser, and stirring was continued at room temperature for 5 h. Saturated aqueous NH_4Cl (10 mL) was added, the mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over

silica gel (2.8 × 20 cm), using 1:19 Et_2O–hexane, gave benzyl ether **251** (237 mg, 77%) as a pure [^1H NMR (300 MHz)], oil: FTIR ($CHCl_3$ cast) 2857, 1604, 1494, 1239, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 3 H), 4.58 (s, 2 H), 4.61 (s, 2 H), 6.87 (dd, J = 8.5, 2.5 Hz, 1 H), 7.14 (d, J = 2.5 Hz, 1 H), 7.28–7.45 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 55.58, 71.27, 72.49, 113.41, 118.00, 123.69, 127.69, 127.83, 128.43, 129.67, 130.43, 138.24, 159.63; exact mass *m/z* calcd for $C_{15}H_{15}{}^{79}BrO_2$ 306.0255, found 306.0266. Anal. Calcd for $C_{15}H_{15}BrO_2$ C, 58.65; H, 4.92; Br, 26.01. Found: C, 58.66; H, 4.89; Br, 26.01.

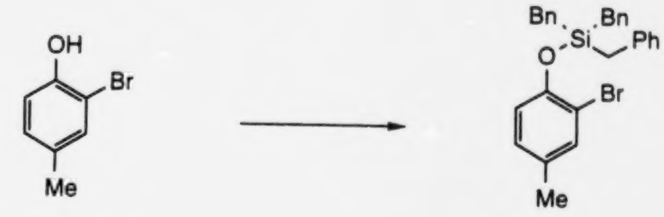
Reduction of 1-(benzyloxymethyl)-2-bromo-4-methoxybenzene (251).



251 **251r**

General procedure (A) for radical reduction of aryl bromides was followed, using bromide **251** (149 mg, 4,85 mmol), Ph_3SnD (342 mg, 9.7 mmol) in dry PhH (9 mL), and AIBN (20 mg, 0.12 mmol) in dry PhH (1.0 mL), with addition over 1.5 h. Flash chromatography of the crude oil over silica gel (1.8 × 12 cm), using 1:19 Et_2O–hexane, gave reduced compound **251r** (82.6 mg, 74 %) as an oil: FTIR ($CHCl_3$ cast) 3030, 2905, 1610, 1584, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3 H), 4.50–4.55 (m, 3.30 H, including s at 4.50 and 4.55), 6.88–6.94 (m, 2 H), 6.27–7.42 (m, 0.70 H); ^2H NMR ($CHCl_3$, 61.24 MHz) δ 4.45 (s, 0.62 ^2H), 7.28 (s, 0.38 ^2H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 55.31 (q), 77.35 (s' J_{CD} = 21 Hz), 71.76 (t), 71.86 (t), 113.75 (d), 113.85 (d), 127.61 (d), 127.83 (d), 128.41 (d), 129.43 (d), 130.44 (s), 138.44 (s), 159.27 (s); exact mass *m/z* calcd for $C_{15}H_{15}DO_2$ 229.1213, found 229.1213.

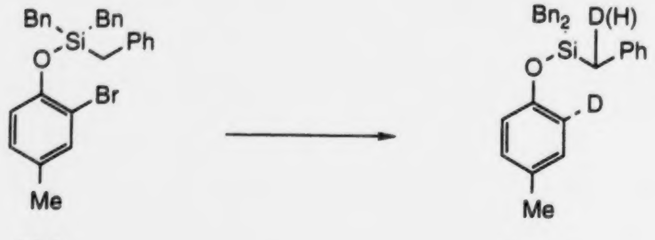
(2-Bromo-4-methyl-1-phenyloxy)tribenzylsilane (252).



241 **252**

Imidazole (0.54 g, 8.0 mmol) was added to a solution of phenol[115] **241** (1.12 g, 6.0 mmol) and $(PhCH_2)_3SiCl$[109a,143] (96%, 1.39 g, 4.0 mmol) in dry THF (40 mL). Stirring was continued at room temperature overnight. Et_2O (200 mL) was added, the mixture was filtered through a pad of Florisil (8.0 × 2.0 cm), the pad was washed twice with Et_2O (2 × 100 mL), and the filtrate were evaporated. Flash chromatography of the residue over silica gel (2.8 × 18 cm), using 1:49 Et_2O–hexane, gave bromide **252** (1.49 g, 76%) as a pure [^1H NMR (300 MHz)], white solid: mp 72–73.5 °C ; FTIR ($CHCl_3$ cast) 3025, 1599, 1492, 1282, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3 H), 2.32 (s, 3 H), 6.11 (d, J = 8.0 Hz, 1 H), 6.80 (ddd, J = 8.0, 2.5, 0.5 Hz, 1 H), 6.96–7.02 (m, 6 H), 7.08–7.16 (m, 3 H), 7.16–7.24 (m, 6 H), 7.32 (dd, J = 2.5, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.26, 23.29, 115.03, 10.40, 124.78, 128.48, 129.04, 132.73, 133.58, 137.33, 149.70; exact mass *m/z* calcd for $C_{28}H_{27}{}^{79}BrOSi$ 486.1015, found 486.1007. Anal. Calcd for $C_{28}H_{27}BrOSi$ C, 68.98; H, 5.58; Br, 16.39, Si, 5.76. Found: C, 69.08; H, 5.46; Br, 16.16.

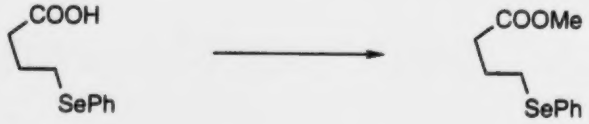
Reduction of (2-bromo-4-methyl-1-phenyloxy)tribenzylsilane (252).



252 **252r**

General procedure (A) for radical reduction of aryl bromides was followed, using bromide **252** (156.4 mg, 0.321 mmol), Ph_3SnD (225.8 mg, 0.64 mmol) in dry PhH (5.4 mL), and AIBN (20 mg, 0.12 mmol) in dry PhH (1 mL), with addition over 1 h. Flash chromatography of the residue over silica gel (1.8 × 17 cm), using 7:93 $CHCl_3$–hexane, gave reduced compound **252r** (47 mg, 36%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR (CH_2Cl_2 cast) 3024, 1600, 1509, 1493, 1451, 1255, 920, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.21–2.31 (m, 8.1 H), 6.47–6.56 (m, 1.9 H), 6.95–7.04 (m, 8 H), 7.06–7.27 (m, 10 H); ^{2}H NMR ($CHCl_3$, 61.423 MHz) δ 2.29 (s, 0.96 ^{2}H), 6.60 (s, 0.04 ^{2}H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.63(q'), 22.79 (d', J_{CD} = 18 Hz), 23.13 (d'), 119.76 (d'), 124.82 (d'), 128.43 (d'), 129.00 (d'), 129.99 (d'), 131.02 (s'), 137.58 (s'), 152.42 (s'); exact mass *m/z* calcd for $C_{28}H_{27}DOSi$ 409.1972, found 409.1978.

Methyl 4-phenylselenobutyrate (266).

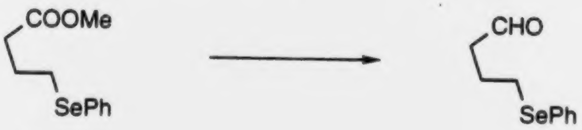


265 **266**

Concentrated H_2SO_4 (*ca.* 10 drops) was added to a stirred solution of crude selenide[122] **265** in MeOH (100 mL). The mixture was heated at 65 °C for 20 h, cooled, and evaporated. The residue was dissolved in Et_2O (200 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL). The organic layer was dried

(Na_2SO_4) and evaporated to give the crude ester **266** (10.05 g, 78.3%) as a reddish oil. Flash chromatography of a small sample over silica gel, using 3:97 EtOAc–hexane, gave pure material: FTIR ($CDCl_3$ cast) 2948, 1736, 1436, 1206, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (pentet, J = 7.0 Hz, 2 H), 2.46 (t, J = 7.0 Hz, 2 H), 2.94 (t, J = 7.0 Hz, 2 H), 3.65 (s, 3 H), 7.20–7.30 (m, 3 H), 7.45–7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 25.31 (t'), 26.99 (t'), 33.69 (t'), 51.57 (q'), 126.93 (d'), 129.08 (d'), 129.88 (s'), 132.71 (d'), 173.32 (s'); exact mass *m/z* calcd for $C_{11}H_{14}O_2{}^{80}Se$ 258.0158, found 258.0164.

4-(Phenylseleno)-butyraldehyde (267).



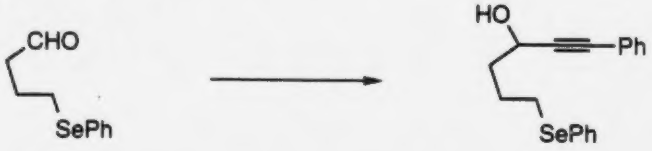
266 **267**

DIBAL-H[200] (10.0 mL, 1.0 M in CH_2Cl_2, 10.0 mmol) was injected dropwise (10 min) into a stirred and cooled (-78 °C) solution of crude ester **266** (2.57 g, 10.0 mmol) in dry CH_2Cl_2 (100 mL). The solution was stirred for 30 min, and $Na_2SO_4 \cdot 10\ H_2O$ (3.22 g, 10.0 mmol) was added. The cooling bath was removed, the mixture was stirred for 60 min and then dried (anhydrous Na_2SO_4, 9.0 g, 63 mmol). The mixture was filtered through a pad of Celite (3 × 10 cm), the pad was washed with CH_2Cl_2 (4 × 75 mL), and the filtrate was evaporated. Flash chromatography of the residue over silica gel (5 × 18 cm), using 3:47 EtOAc–hexane, gave aldehyde **267** (1.974 g, 87%) as a pure [^1H NMR (300 MHz)], slightly yellow oil: FTIR ($CDCl_3$ cast) 2824, 1723, 1578, 1478, 1437, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.99 (pentet, J = 7.0 Hz, 2 H), 2.56 (td, J = 7.0, 1.5 Hz, 2 H), 2.92 (t, J = 7.0 Hz, 2 H), 7.19–7.30 (m, 3 H), 7.4–7.54 (m, 2 H), 9.73 (t, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 22.45 (t'), 26.97 (t'), 43.45 (t'), 126.97

(d'), 129.09 (d'), 129.64 (s'), 132.63 (d'), 201.34 (d'); exact mass *m/z* calcd for $C_{10}H_{12}O^{80}Se$ 228.0053, found 228.0048.

General Procedure for Addition of an Acetylide to an Aldehyde.[121] The acetylene was placed in a round-bottomed flask sealed with a rubber septum and equipped with a Teflon-coated stirring bar. The system was flushed with Ar for 2–5 min, and dry THF was injected. The solution was lowered into a cooling bath (-78 °C) and stirred for 5 min. A solution of *n*-BuLi (Aldrich, 1.6 M in hexanes) was injected dropwise, the mixture was stirred at -78 °C for 5–15 min, and a solution of the aldehyde in dry THF was then injected at a rapid dropwise rate. Stirring was continued at -78 °C for 15–45 min, and the mixture was then quenched with saturated aqueous NH_4Cl or 10% aqueous $KHSO_4$. The cooling bath was removed, the mixture was allowed to reach room temperature, and then processed as described for the individual experiments.

1-Phenyl-6-(phenylseleno)-1-heptyn-3-ol (269).

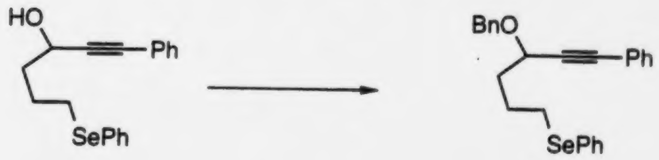


267 **269**

The general procedure for addition of an acetylide to an aldehyde was followed, using phenylacetylene **268** (2.96 mg, 2.90 mmol) in THF (15 mL), *n*-BuLi (1.64 mL, 1.6 M in hexanes, 2.62 mmol), an initial reaction period of 15 min, and aldehyde **267** (379.5 g, 1.75 mmol) in THF (1.5 mL plus 1.0 mL as a rinse). Stirring was continued for 45 min. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 20 cm), using 1:9 EtOAc–hexane, gave alcohol **269** (454.7 mg, 79%) as a pure [^1H NMR (300 MHz)], colorless oil: FTIR

($CDCl_3$ cast) 3362, 2936, 1578, 1489, 1477, 1437, 757, 735, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1,86–2.01 (m, 4 H), 2.08 (br s, 1 H), 2.89–3.03 (m, 2 H), 4.60 (br s , 1 H), 7.17–7.33 (2 m, 6 H), 7.33–7.42 (m, 2 H), 7.45, 7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 25.82 (t'), 27.51 (t'), 37.71 (t'), 62.43 (d'), 85.24 (s'), 89.73 (s'), 122.49 (s'), 126.83 (d'), 128.31 (d'), 128.48 (d'), 129.06 (d'), 130.20 (s'), 131.71 (d'), 132.72 (d'); exact mass *m/z* calcd for $C_{18}H_{18}O^{80}Se$ 330.0522, found 330.0527. Anal. Calcd for $C_{18}H_{18}OSe$: C, 65.65; H, 5.51. Found: C, 65.48; H, 5.53.

3-Bezyloxy-1-phenyl-6-(phenylseleno)-1-hexyne (270).

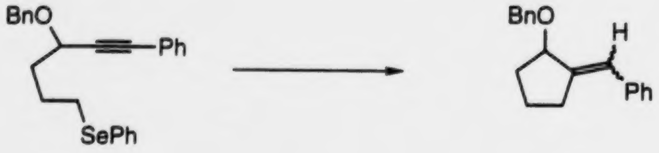


269 **270**

NaH (60% dispersion in oil, 120 mg, 3.00 mmol) was added to a stirred solution of benzyl bromide (0.36 mL, 3.0 mmol) and alcohol **269** (493 mg, 1.50 mmol). Stirring was continued at room temperature overnight. Saturated aqueous NH_4Cl (5 mL) was carefully added, the mixture was diluted with water (50 mL), and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using increasing amounts of Et_2O in hexane (from 0% to 2%), gave **270** (495.7 mg, 79%) as an pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 3059, 3030, 2942, 2929, 2859, 1579, 1092, 1071, 756, 735, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.79–1.96 (m, 4 H), 2.80–2.90 (m, 2 H). 4.19–4.27 (m, 1 H), 4.46 (d, *J* = 11.5 Hz, 1 H), 4.75 (d, *J* = 11.5 Hz, 1 H), 7.08–7.15 (m, 3 H), 7.15–7.30 (m, 8 H), 7.30–7.35 (m, 2 H), 7.35–7.43 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 25.95 (t'), 27.53 (t'), 35.72 (t'), 68.58 (d'), 70.61 (t'), 86.28 (s'), 87.90 (s'), 122.68 (s'), 126.72 (d'), 127.67 (d'), 127.98 (d'), 128.28

(d'), 128.38 (d'), 128.99 (d'), 130.29 (s'), 131.77 (d'), 132.66 (d'), 138.00 (s'); exact mass *m/z* calcd for $C_{25}H_{24}OSe$ 420.0993, found 420.0988.

2-(Benzyloxy)-1-(phenylmethylene)cyclopentane (271).



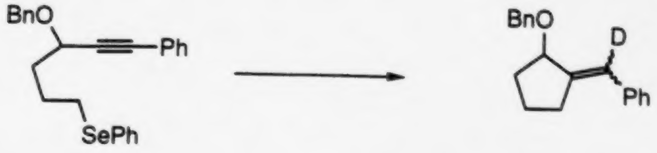
270 **271**

A solution of AIBN (3.30 mg, 0.02 mmol) in dry PhH (2.5 mL) and a solution of Ph_3SnH (84.3 mg, 0.24 mmol) in dry PhH (2.5 mL) were added (syringe pump) to a stirred and refluxing solution of selenide **270** (83.9 mg, 0.20 mmol) in dry PhH (20 mL) over 10 h. Refluxing was continued for 6 h after the addition, and the mixture was then cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (1.8 × 13 cm), using increasing amounts of $CHCl_3$ in hexane (from 20% to 40%), gave cyclized ether **271** (5.1 mg, 10%) as a oil. The data [^1H NMR and ^{13}C NMR] indicated the presence of two isomers†: FTIR ($CDCl_3$ cast) 3025, 2956, 1495, 1452, 1064, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61–2.19 (m, 4 H), 2.34–2.63 (m, 1 H), 2.63–2.79 (m, 1 H), 4.30 (t, $J = 5.0$ Hz, 0.82 H), 4.44–4.66 (m, 2.18 H), 6.55–6.59 (m, 1 H), 7.17–7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.465 MHz) δ 22.33* (t'), 23.05 (t'), 28.88 (t'), 31.85 (t'), 32.30* (t'), 33.20* (t'), 69.80* (t'), 70.09 (t'), 78.30* (d'), 84.02 (d'), 125.45 (d'), 126.56 (d'), 127.44 (d'), 127.59 (d'), 127.74 (d'), 128.22 (d'), 128.27 (d'), 128.40 (d'), 128.52 (d'), 128.63 (d'). 137.86 (s'), 139.01 (s'), 144.08 (s'); exact mass *m/z* calcd for $C_{19}H_{20}O$ 264.1514, found 264.1515.

† None of the signals in the ^{13}C NMR spectrum corresponds to the reduced compound (non-cyclized), by comparison to an authentic sample.

* Carbon signal of the minor isomer.

2-(Benzyloxy)-1-([1-$^2H_1$]-phenylmethylene)cyclopentane (272).



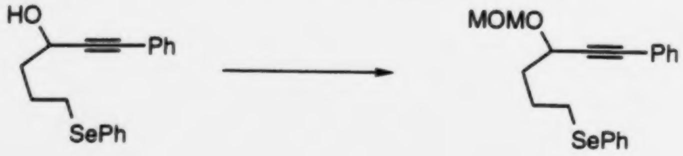
270 **272**

A solution of AIBN (3.3 mg, 0.02 mmol) in dry PhH (0.5 mL plus 0.5 mL as a rinse) was added to a stirred and refluxing mixture of selenide **270** (83.9 mg, 0.20 mmol) and Ph_3SnD (84.5 mg, 0.24 mmol) in dry PhH (9 mL). Stirring was continued at 80 °C for 22 h, and the mixture was then cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using increasing amounts of CH_2Cl_2 in hexane (from 10% to 30%), gave benzyl ether **272** (13.1 mg, 24%) as a oil. The data [^{1}H NMR and ^{13}C NMR] indicated the presence of two isomers†: FTIR ($CDCl_3$ cast) 3026, 2957, 1494, 1064, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65–1.94 (m, 3 H), 1.94–2.21 (m, 1 H), 2.36–2.63 (m, 1 H), 2.63–2.79 (m, 1 H), 4.30–4.36 (m, 0.75 H), 4.46–4.68 (m, 2.25 H), 7.17–7.46 (m, 10 H); ^{2}H NMR ($CHCl_3$, 61.423 MHz) δ 6.62 (s, 1.0 ^{2}H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 22.30* (t'), 23.06 (t'), 28.86 (t'), 31.86 (t'), 32.30* (t'), 33.22* (t'), 69.82* (t'), 70.10 (t'), 78.31* (d'), 84.01 (d'), 125.15* (d'), 126.57 (d'), 127.46 (d'), 127.61 (d'), 127.74 (d'), 128.23 (d'), 128.28 (d'), 128.40 (d'), 128.52 (d'), 128.63 (d'), 137.81 (s'), 139.02 (s'), 144.51 (s'); exact mass *m/z* calcd for $C_{19}H_{19}DO$ 265.1577, found 265.1573.

† None of the signals in the ^{13}C NMR spectrum corresponds to the reduced compound (non-cyclized), by comparison to an authentic sample.

* Carbon signal of the minor isomer.

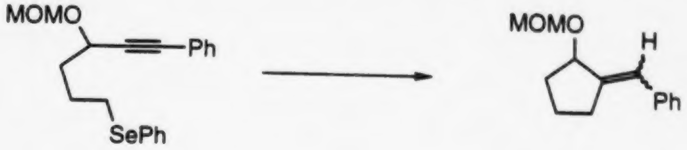
3-(Methoxymethoxy)-1-phenyl-6-(phenylseleno)-1-hexyne (273).



269 **273**

NaH (60% dispersion in oil, 120 mg, 3.0 mmol) was added to a stirred solution of CH_3OCH_2Cl (0.24 mL, 3.2 mmol) and alcohol **269** (493 mg, 1.50 mmol).[194] Stirring was continued at room temperature overnight. Saturated aqueous NH_4Cl (5 mL) was carefully added, and the mixture was diluted with water (100 mL), and then extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 14 cm), using increasing amounts of Et_2O in hexane (from 2% to 4%), gave methoxymethyl ether **273** (436.1 mg, 58%) as a pure [^1H NMR (300 MHz)], colorless oil: FTIR (CH_2Cl_2 cast) 3054, 2946, 1578, 1490, 1478, 1438, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.89–2.03 (m, 4 H), 2.91–3.02 (m, 2 H), 3.36 (s, 3 H), 4.51–4.58 (m, 1 H), 4.61 (d, J = 7.0 Hz, 1 H), 4.99 (d, J = 7.0 Hz, 1 H), 7.17–7.25 (m, 3 H), 7.25–7.34 (m, 3 H), 7.34–7.42 (m, 2 H), 7.45–7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 26.03 (t'), 27.58 (t'), 35.75 (t'), 55.95 (q'), 65.66 (d'), 85.88 (s'), 97.48 (s'), 97.27 (t'), 122.61 (s'), 126.83 (d'), 128.28 (d'), 128.43 (d'), 129.05 (d'), 130.27 (s'), 131.81 (d'), 132.79 (d'); exact mass *m/z* calcd for $C_{20}H_{22}O_2Se$ 374.0785, found 374.0791. Anal. Calcd for $C_{20}H_{22}O_2Se$ C, 64.34; H, 5.94. Found: C, 64.19; H, 5.72.

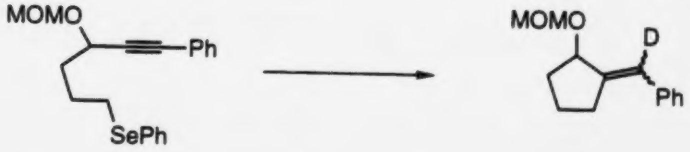
2-(Methoxymethoxy)-1-(phenylmethylene)cyclopentane (274).



273 **274**

A solution of AIBN (8.3 mg, 0.05 mmol) in dry PhH (0.5 mL plus 0.5 mL as a rinse) was injected rapidly into a refluxing solution of Ph_3SnH (105 mg, 0.30 mmol) and selenide **273** (74.7 mg, 0.20 mmol) in dry PhH (9 mL). Refluxing was continued overnight, the mixture was cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:49 Et_2O–hexane, gave cyclization compounds **274** (41.9 mg, 90%) as a mixture of isomers: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.67–2.09 (m, 4 H), 2.34–2.47 (m, 0.08 H), 2.48–2.78 (m, 1.92 H), 3.32 (s, 0.24 H), 3.43 (s, 2.76 H), 4.45–4.51 (m, 1 H), 4.64 (d, *J* = 7.0 Hz, 0.08 H), 4.70 (d, *J* = 7.0 Hz, 0.92 H), 4.72 (d, *J* = 7.0 Hz, 0.08 H), 4.82 (d, *J* = 7.0 Hz, 0.92 H), 6.55 (s, 0.92 H), 5.65 (s, 0.08 H), 7.15–7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 21.92* (t'), 22.98 (t'), 28.89 (t'), 32.31 (t'), 32.98* (t'), 33.57* (t'), 55.38 (q'), 55.97* (q'), 81.43 (d'), 94.53 (t'), 125.16 (d'), 126.58 (d'), 128.26 (d'), 128.59 (d'), 137.81 (s'), 144.27 (s'); exact mass *m/z* calcd for $C_{14}H_{18}O_2$ 218.1306, found 218.1311.

2-(Methoxymethoxy)-1-([1-$^2H_1$]-phenylmethylene)cyclopentane (275).

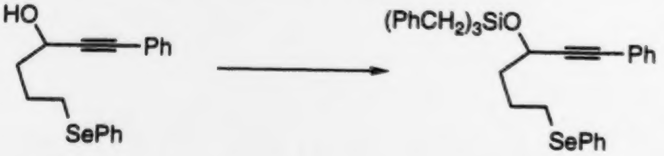


273 **275**

A solution of AIBN (8.3 mg, 0.05 mmol) in dry PhH (0.5 mL plus 0.5 mL as a rinse) was injected rapidly into a refluxing solution of Ph_3SnD (106 mg, 0.30 mmol) and selenide **273** (74.7 mg, 0.20 mmol) in dry PhH (9 mL). Refluxing was continued overnight, and the mixture was cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:49 Et_2O–hexane, gave cyclization compounds **275** (40.1 mg, 91%) as a mixture of isomers: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66–2.07 (m, 4 H), 3.33 (s, 0.24 H), 3.42 (s, 2.76 H), 4.48 (m, 1 H), 4.64 (d, *J* = 7.0 Hz, 0.08 H), 4.70 (d, *J* = 7.0 Hz, 0.92 H), 4.72 (d, *J* = 7.0 Hz, 0.08 H), 4.82 (d, *J* = 7.0 Hz, 0.92 H), 6.66 (s, 0.08 H, residual Ph_3SnH), 7.14–7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 22.98 (t'), 28.96 (t'), 32.31 (t'), 55.37 (q'), 81.40 (d'), 94.52 (t'), 125.15* (d'), 126.58 (d'), 128.26 (d') 128.57 (d'), 137.75 (s'), 144.15 (s'); exact mass *m/z* calcd for $C_{14}H_{17}DO_2$ 219.1370, found 219.1367.

* The marked carbon (125.15*) has 20% of the intensity of the signal at 126.58.

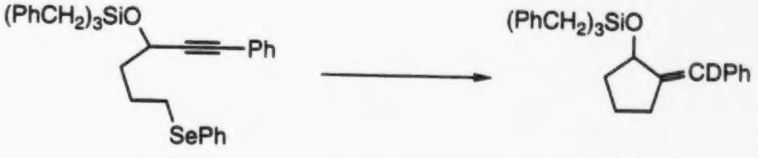
[3-[1-Phenyl-6-(phenylseleno)-1-hexynyl]oxy]tribenzylsilane (276).



269 **276**

Imidazole (68 mg, 1.0 mmol) was added to a stirred mixture of $(PhCH_2)_3SiCl$[109a,143] (186 mg, 0.535 mmol) and alcohol **269** (165 mg, 0.27 mmol) in dry THF (10 mL). The mixture was stirred at room temperature overnight, Et_2O (100 mL) was added, and the mixture was filtered through a pad of Florisil (3 × 3 cm). The pad was washed with Et_2O (2 × 50 mL), and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.8 × 13 cm), using 1:9 $CHCl_3$–hexane, gave silyl ether **276** (245.9 mg, 78%) as a pure [^1H NMR (300 MHZ)], colorless oil: FTIR ($CDCl_3$ cast) 3023, 2924, 1598, 1494, 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.75–1.86 (m, 4 H), 2.19–2.32 (m, 6 H), 2.83–2.92 (m, 2 H), 4.52–4.58 (m, 1 H), 6.98–7.14 (m, 9 H), 7.14–7.25 (m, 9 H), 7.28–7.34 (m, 3 H), 7.34–7.40 (m, 2 H), 7.45–7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 23.38 (t'), 25.58 (t'), 27.60 (t'), 38.33 (t'), 63.42 (d'), 85.88 (s'), 90.16 (s'), 122.61 (s'), 124.53 (d'), 126.78 (d'), 128.35 (d'), 128.50 (d'), 128.98 (d'), 129.06 (d'), 130.44 (s'), 131.60 (d'), 132.68 (d'), 138.19 (s'); exact mass *m/z* calcd for $C_{39}H_{39}O^{80}SeSi$ 630.1844, found 630.1857.

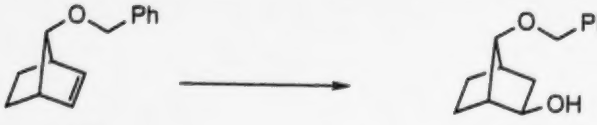
[2-([1-$^2H_1$]Phenylmethylene)cyclopentyl]oxytribenzylsilane (277).



276 **277**

A solution of AIBN (18 mg, 0.11 mmol) in dry PhH (1 mL) was slowly added (syringe pump) to a stirred and refluxing solution of silyl ether **276** (169 mg, 0.27 mmol) and Ph_3SnD (243.3 mg, 0.69 mmol) in dry PhH (6 mL) over 2 h. The mixture was cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using 3:17 $CHCl_3$–hexane. The isolated product contained stannane residues, and was further purified by flash chromatography over silica gel (1.8 × 13 cm), using 1:99 Et_2O–hexane, and gave cyclopentane **277** (64.6 mg, 50%) as a oil: FTIR ($CDCl_3$ cast) 3000, 1598, 1494, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.49–1.85 (m, 3 H), 1.89–2.04 (m, 1 H), 2.28 (s, 6 H), 2.51–2.77 (m, 2 H), 4.64 (t, $J = 6.0$ Hz, 1 H), 6.30 (m, 0.20 H), 7.06–7.44 (m, 20 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 21.79 (t'), 23.67 (t'), 28.33 (t'), 34.75 (t'), 78.19 (d'), 123.11 (d'), 124.52 (d'), 126.34 (d'), 128.24 (d'), 128.34 (d'), 128.49 (d'), 129.01 (d'), 137.91 (s'), 138.35 (s'), 146.11 (s'), 146.22 (s'); exact mass *m/z* calcd for $C_{33}H_{33}DOSi$ 475.2442, found 475.2440.

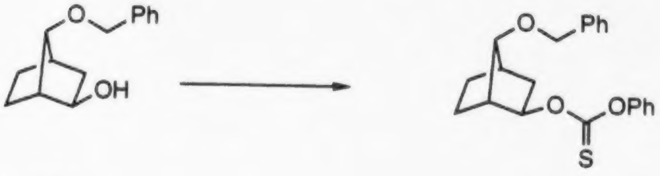
(*exo*,*syn*)-(±)-7-(Benzyloxy)-bicyclo[2.2.1]heptan-2-ol (289).



288 **289**

$BH_3 \cdot THF$[129] (6.9 mL, 1.0 M in THF, 6.9 mmol) was added to a stirred and cooled (0 °C) solution of ether **288** (1.12 g, 5.6 mmol) in dry THF (25 mL). The cooling bath was removed, and stirring was continued at room temperature for 5 h. Aqueous NaOH (2.0 N, 7 mL) and 30% H_2O_2 (7 mL) were carefully added to the mixture, and stirring was continued at room temperature overnight. Water (100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 15 cm), using increasing amounts of EtOAc in hexanes (from 20% to 25%), gave alcohol **289** (406.6 mg, 33%) as a pure [^{1}H NMR (300 MHz)], white solid: mp 105–109 °C; FTIR ($CDCl_3$ cast) 3345, 2959, 2875, 1454, 1419, 1356, 1195, 741, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98–1.16 (m, 2 H), 1.37–1.63 (m, 2 H), 1.66–1.86 (m, 1 H), 1.95 (dd, *J* = 14.5, 7.0 Hz, 1 H), 2.26 (d, *J* = 4.0 Hz, 1 H), 2.35–2.42 (m, 1 H), 2.40–3.15 (br s, 1 H), 3.75 (d, *J* = 7.0, 1 H), 3.83 (s, 1 H), 4.50 (d, *J* = 11.5 Hz, 1 H), 4.60(d, *J* = 11.5 Hz, 1 H), 7.25–7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 21.63 (t'), 25.09 (t'), 45.25 (d'), 71.87 (t'), 76.08 (d'), 87.63 (d'), 127.70 (d'), 127.85 (d'), 128.55 (d'), 137.97 (s'); exact mass *m/z* calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1307.

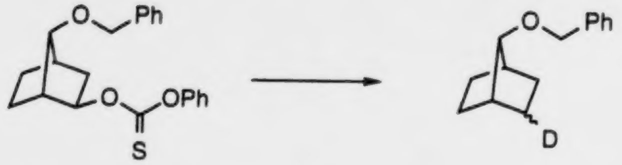
Thioacylation of (*exo,syn*)-(±)-7-(benzyloxy)-bicyclo[2.2.1]heptan-2-ol (289).



289 **290**

Phenyl chlorothionoformate[109a,131] (0.22 g, 1.3 mmol) was added to a stirred solution of alcohol **289** (98.5 mg, 0.45 mmol) and pyridine (0.18 g, 2.2 mmol) in dry CH_2Cl_2 (10 mL). Stirring was continued at room temperature overnight. CH_2Cl_2 (100 mL) was added, and the mixture was washed with 2.0 N aqueous HCl (20 mL) and water (20 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 10 cm), using 3:97 EtOAc–hexane, gave thiocarbonyl ester **290** (153.8 mg, 96%) as a solid: mp 63–65 °C; FTIR ($CHCl_3$ cast) 2966, 1490, 1328, 1282, 1193 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09–1.20 (m, 1 H), 1.20–1.34 (m, 1 H), 1.51–1.74 (m, 2 H), 2.08 (dd, J = 13.5, 7.5 Hz, 1 H), 2.20–2.46 (m, 2 H), 2.74 (d, J = 4.0 Hz, 1 H), 3.81 (s, 1 H), 4.41 (d, J = 11.5 Hz, 1 H), 5.19 (dd, J = 7.5, 3.0 Hz, 1 H), 7.05–7.14 (m, 2 H), 7.21–7.47 (m, 8 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.20 (t'), 24.50 (t'), 37.39 (t'), 38.96 (d'), 41.85 (d'), 71.48 (t'), 85.69 (d'), 87.19 (d'), 122.10 (d'), 126.37 (d'), 127.55 (d'), 127.95 (d'), 128.37 (d'), 129.46 (d'), 138.50 (s'), 153.51 (s'); exact mass *m/z* calcd for $C_{14}H_{15}O_3S$ ($M^+ - C_7H_7$) 201.1279, found 201.1281. Anal. Calcd for $C_{21}H_{22}O_3S$ C, 71.16; H, 6.26; S, 9.04. Found: C, 71.03; H, 6.33; S, 9.19.

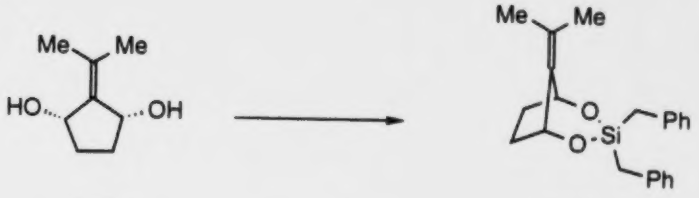
(*syn*)-(±)-7-(Benzyloxy)-[2-$^{2}H_{1}$]bicyclo[2.2.1]heptane (291).



290 **291**

A solution of AIBN (*ca.* 10 mg) in dry PhH (0.5 mL) was slowly added (syringe pump) to a stirred and refluxing solution of Ph_3SnD (161 mg, 0.46 mmol) and thiocarbonyl ester **290** (70.9 mg, 0.20 mmol) in dry benzene (3.5 mL) over 2 h. The reflux was maintained for 2 h after the addition. The mixture was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (1.8 × 12 cm), using 1:99 Et_2O–hexane, gave reduced compound **291** (25.2 mg, 62%) as an oil containing some stannane residues, which do not interfere with the spectral interpretation: FTIR ($CHCl_3$ cast) 2953, 2871, 1720, 1453, 1355, 1148, 1113, 1100, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13–1.33 (m, 3.77 H), 1.49–1.61 (m, 2 H), 1.80–1.92 (m, 1.23 H), 2.09–2.17 (m, 2 H), 3.71 (s, 1 H), 4.50 (s, 2 H), 7.20–7.44 (m, 5 H); ^{2}H NMR ($CHCl_3$, 64.423 MHz) δ 1.26 (s, 0.16 ^{2}H), 1.88 (s, 0.84 ^{2}H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 26.53 (t'), 26.63 (t'), 26.94 (d', J_{CD} = 19.6 Hz), 27.26 (residual CH_2); 37.84 (d'), 37.91 (d'), 71.20 (t'), 85.35 (d'), 127.41 (d'), 127.59 (d'), 128.36 (d'), 139.08 (s'); exact mass *m/z* calcd for $C_{14}H_{17}DO$ 203.1420, found 203.1415.

3,3-Dibenzyl-8-(1-methylethylidene)-2,4-dioxa-3-silabicyclo[3.3.1]octane (299).

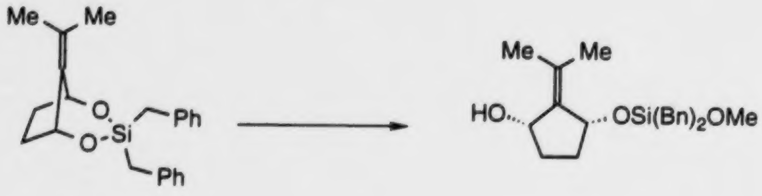


298 **299**

A solution of diol[132a] **298** (258 mg, 1.81 mmol) in dry THF (20 mL), and a solution of $(PhCH_2)_2SiCl_2$[134] (510 mg, 1.81 mmol) were added simultaneously (syringe pump) to a stirred solution of imidazole (0.62 g, 9.1 mmol) in dry THF (160 mL) at 65 °C over a period of 2.5 h. The mixture was cooled to room temperature, and Et_2O (400 mL) was added. The mixture was filtered through a pad of Florisil (7 × 3 cm), the pad was washed with ether (100 mL), and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using 1:19 Et_2O–hexane, gave cyclic ether **299** (301.4 mg, 47%) as a homogeneous [^{1}H NMR (300 MHz)], white solid: mp 72–73.5 °C; FTIR ($CDCl_3$ cast) 3024, 2933, 1493, 1161, 1038, 998, 904, 807, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49–1.61 (m, 4 H), 1.63 (s, 6 H), 2.08 (2 s, 4 H), 4.77–4.82 (m, 2 H), 7.01–7.14 (m, 6 H), 7.18–7.27 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.51 (q'), 25.42 (t'), 26.58 (t'), 32.60 (t'), 74.24 (d'), 124.34 (d'), 124.54 (d'), 128.11 (d'), 128.22 (s'), 128.33 (d'), 128.80 (d'), 129.02 (d'), 137.29 (s'), 137.64 (s'), 138.07 (s'); exact mass *m/z* calcd for $C_{22}H_{26}O_2Si$ 350.1702, found 350.1706. Anal. Calcd for $C_{22}H_{26}O_2Si$ C, 75.38; H, 7.48. Found: C, 75.53; H, 7.42. Molecular weight (osmometry, benzene solution) calculated 350.53, found 338.5.

A similar experiment, setting the reaction temperature at 0 °C, gave ether **299** (272.6 mg, 43%).

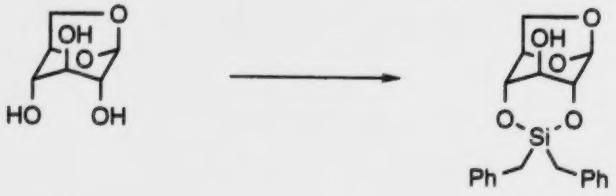
(±)-(1*R**,3*S**)-3-[(Dibenzylmethoxysilyl)oxy]-2-(1-methylethylidene)cyclopentanol (300).



299 **300**

A solution of protected diol **299** (71.0 mg, 0.20 mmol) in dry MeOH (4 mL) was stirred at room temperature for 3 h. Evaporation of MeOH, and flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 EtOAc–hexane, gave alcohol **300** (71.1 mg, 92%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 3432, 2935, 1494, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50–1.66 (m, 1 H), 1.68–1.86 (m, 9 H, including 1.72 [s, 3 H] and 1.83 [s, 3 H]), 1.88–2.03 (m, 1 H), 2.17 (s, 2 H), 2.18 (s, 2 H), 3.43 (s, 3 H), 4.50 (s, 3 H), 4.50–4.58 (m, 1 H), 4.76 (dd, *J* = 5.0, 2.0 Hz, 1 H), 7.03–7.14 (m, 6 H), 7.17–7.25 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.84 (q'), 21.14 (q'), 22.59 (t'), 33.54 (t'), 51.03 (q'), 71.98 (d'), 73.18 (d'), 124.62 (d'), 128.30 (d'), 128.96 (d'), 133.53 (s'), 137.75 (s'), 140.16 (s'); exact mass *m/z* calcd for $C_{23}H_{28}O_2Si$ (M - H_2O)$^+$ 364.1585, found 364.1849.

1,6-Anhydro-2,4-*O*-(dibenzylsilyl)-β-D-glucopyranoside (304).

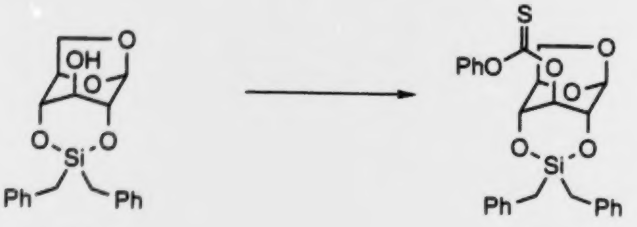


303 **304**

A solution of 1,6-anhydro-β-D-glucopyranose **303**^{109b,138} (162.1 mg, 1.00 mmol) in a mixture 1:1 of dry THF–DMF (5 mL) and a solution of $(PhCH_2)_2SiCl_2$^{134} (350 mg, 1.25 mmol) in dry THF (5 mL) were simultaneously added to a stirred and cooled (0

°C) solution of imidazole (340 mg, 5.00 mmol) in dry THF (40 mL) over a period of 6 h. The cooling bath was removed, and stirring was continued at room temperature overnight. The mixture was filtered through a pad of Florisil (2 × 3 cm), the pad was washed with EtOAc (3 × 25 mL), and the filtrate was evaporated (most DMF remained). Flash chromatography of the residue over silica gel (1.8 × 15 cm), using 1:3 EtOAc–hexane, gave alcohol **304** (189.5 mg, 51%) as a homogeneous [^{1}H NMR (300 MHz)] white solid: mp 171–173 °C; $[\alpha]^{20}_D$ -31.6 (*c* = 2.4, CH_2Cl_2); FTIR ($CHCl_3$ cast) 3406, 2938, 1599, 1494, 1451, 1212, 1135, 1075, 913, 821, 808, 778, 701 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 2.13 (s, 2 H), 2.48 (s, 2 H), 2.82 (d, *J* = 8.5 Hz, 1 H), 2.98 (doublet of pentets, *J* = 8.5, 2.5 Hz, 1 H), 3.69 (q, *J* = 2.5 Hz, 1 H), 3.77 (dd, *J* = 8.0, 5.0 Hz, 1 H), 3.81 (q, *J* = 2.5 Hz, 1 H), 4.28 (d, *J* = 8.0 Hz, 1H) 4.61 (dt, *J* = 5.0, 2.5 Hz, 1 H), 5.54 (t, *J* = 2.5 Hz, 1 H), 7.00–7.17 (m, 6 H), 7.18–7.29 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 25.54 (t'), 26.13 (t'), 65.48 (t'), 71.04 (d'), 71.43 (d'), 72.39 (d'), 77.10 (d'), 102.37 (d'), 124.83 (d'), 124.94 (d'), 128.52 (d'), 128.75 (d'), 129.27 (d'), 129.35 (d'), 137.91 (s'), 138.15 (s'); exact mass *m/z* calcd for $C_{20}H_{22}O_5Si$ 370.1237, found 370.1221. Anal. Calcd for $C_{20}H_{22}O_5Si$ C, 64.84; H, 5.99. Found: C, 64.74; H, 6.02.

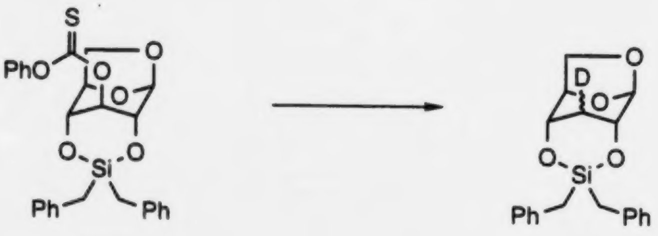
Thioacetylation of 1,6-anhydro-2,4-*O*-(dibenzylsilyl)-β-D-glucopyranoside (304).



304 **305**

Phenyl chlolothionoformate[131] (0.14 mL, 1.0 mmol) was added to a stirred solution of alcohol **304** (185.3 mg, 0.50 mmol) and DMAP (152.7 mg, 1.25 mmol) in dry CH_3CN (20 mL).[125] Stirring was continued at room temperature for 48 h. Et_2O (100 mL) was added, and the mixture was filtered through a pad of Florisil (2 × 3 cm). The pad was washed with Et_2O (2 × 50 mL), and the filtrate was evaporated. Flash chromatography of the residue over silica gel (2.8 × 10 cm), using 1:9 Et_2O–hexane, gave thiocarbonyl ester **305** (112.3 mg, 44%) as a solid: mp 145–147.5 °C; $[\alpha]^{20}_{D}$ -23.0 (*c* = 3.0, CH_2Cl_2); FTIR ($CHCl_3$ cast) 1491, 1278, 1203, 1146, 1114, 1102, 1063, 811 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.19 (s, 2 H), 2.55 (s, 2 H), 3.80 (dd, *J* = 8.0, 5.0 Hz, 1 H), 4.05 (q, *J* = 2.5 Hz, 1 H), 4.11 (q, *J* = 2.5 Hz, 1 H), 4.14 (d, *J* = 8.0 Hz, 1 H), 4.63 (m, *J* = 2.5 Hz, 1 H), 4.70 (p, *J* = 2.0 Hz, 1 H), 5.55 (t, *J* = 2.0 Hz, 1 H), 6.98–7.21 (m, 10 H), 7.22–7.34 (m, 3 H), 7.38–7.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.48 (t'), 26.18 (t'), 65.09 (t'), 68.74 (d'), 69.69 (d'), 76.79 (d'), 78.23 (d'), 101.24 (d'), 122.13 (d'), 124.93 (d'), 125.03 (d'), 127.09 (d'), 128.78 (d'), 128.84 (d'), 129.28 (d'), 129.33 (d'), 129.96 (d'), 137.37 (s'), 137.90 (s'), 153.61 (s'), 193.31 (s'); exact mass *m/z* calcd for $C_{20}H_{19}O_6SSi$ (M^+ - C_7H_7) 415.0672, found 415.0666. Anal. Calcd for $C_{27}H_{26}O_6SSi$ C, 64.01; H, 5.17. Found: C, 63.68; H, 4.90.

1,6-Anhydro-2,4-*O*-(dibenzylsilyl)-3-deoxy-β-D-[3-$^2H_1$]-ribopyranoside (306).

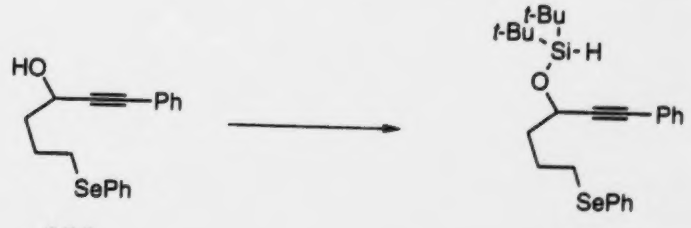


305 **306**

A solution of Bu_3SnD (25 mg, 0.086 mmol) in PhH (1 mL) and a solution of AIBN (2 mg, 0.012 mmol) in PhH (1 mL) were added simultaneously (syringe pump) to a stirred and refluxing solution of thiocarbonyl ester **305** (22.0 mg, 0.043 mmol) in PhH (8 mL) over a period of 2.5 h. Stirring was continued at 80 °C for 30 min. The mixture was cooled to room temperature, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1 × 7 cm), using 1:4 Et_2O–hexane, gave the reduced compound **306** (8.6 mg, 56%) as a white solid: mp 105–108 °C; FTIR ($CHCl_3$ cast) 1599, 1493, 1151, 1113, 821, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87–0.96 (m, 0.76 H), 1.65–1.71 (m, 0.24 H), 2.13 (s, 2 H), 2.47 (s, 2 H), 3.67–3.85 (m, 4 H), 5.38–5.41 (m, 1 H), 7.01–7.28 (m, 10 H); ^2H NMR (CH_2Cl_2, 61.423 MHz) δ 0.94 (s, 0.24 ^2H), 1.70 (s, 0.76 ^2H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.59 (t'), 26.61 (t'), 29.75(d', J_{CD} = 19 Hz), 65.65 (t'), 69.94 (d'), 70.45 (d'), 77.37 (d'), 102.01 (d'), 124.61 (d'), 124.78 (d'), 125.04 (d'), 128.39 (d'), 128.66 (d'), 128.80 (d'), 129.29 (d'), 129.43 (d'), 138.29 (s'), 138.34 (s'); exact mass *m/z* calcd for $C_{13}H_{14}DO_4Si$ $(M - C_7H_7)^+$ 264.0802, found 264.0800.

General Procedure for Silylation of Alkynols. The substrate and imidazole were placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser that was sealed with a rubber septum. The system was flushed with Ar for 2–5 min, and dry THF or dry PhH was injected. A solution of the dialkylchlorosilane (*t*-Bu_2SiHCl, Aldrich; *i*-Pr_2SiHCl, Aldrich; Ph_2SiHCl, Hüls) in dry THF or PhH was injected. A white precipitate was formed, and the reaction mixture was refluxed for 1.75–2.5 h. The mixture was cooled, and processed as described for the individual experiments.

[3-[1-Phenyl-6-(phenylseleno)-1-hexynyl]oxy]di-*tert*-butylsilane (309).



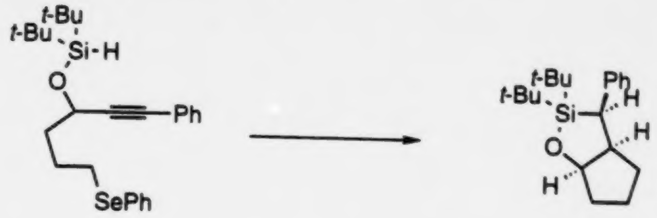
269 **309**

The general procedure for silylation of alkynols was followed, using alcohol **269** (239.3 mg, 1.00 mmol), imidazole (136.2 mg, 2.00 mmol) in THF (8 mL), and *t*-

Bu_2SiHCl (223.5 mg, 1.25 mmol) in THF (1 mL plus 1 mL as a rinse).[146] The mixture was heated for 2.5 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 3:47 CH_2Cl_2–hexane, gave silyl ether **309** (427.8 mg, 91%) as a pure [^1H NMR (400 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2929, 2856, 2096, 1470, 1084, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 9 H), 1.05 (s, 9 H), 1.88–2.04 (m, 4 H), 2.99 (t, J = 7.0 Hz, 2 H), 4.14 (s, 1 H), 4.70 (t, J = 5.5 Hz, 1 H), 7.20–7.25 (m, 3 H), 7.26–7.34 (m, 3 H), 7.35–7.41 (m, 2 H), 7.48–7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.83 (s'), 20.16 (s'), 25.72 (t'), 27.35 (q'), 27.38 (q'), 27.78 (t'), 38.38 (t'), 66.25 (d'), 85.19 (s'), 99.00 (s'), 123.04 (s'), 126.77 (d'), 128.18 (d'), 128.25 (d'), 129.04 (d'), 130.35 (s'), 130.60 (d'), 132.77 (d'); exact mass *m/z* calcd for $C_{26}H_{36}O^{80}SeSi$ 472.1701, found 472.1696. Anal. Calcd for $C_{26}H_{36}OSeSi$: C, 66.22; H, 7.69. Found: C, 66.08; H, 7.82.

General Procedure for Radical Cyclization. The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser that was sealed with a rubber septum. The system was flushed with Ar for 5–10 min, and dry PhH was injected. The solution was refluxed, and separate solutions of Ph_3SnH (Aldrich) or Bu_3SnD (Aldrich) and AIBN, each in dry PhH, were injected simultaneously by syringe pump over 2 h. Refluxing was continued for an arbitrary period of 0.5–2 h after the addition was complete. The reaction mixture was cooled, and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

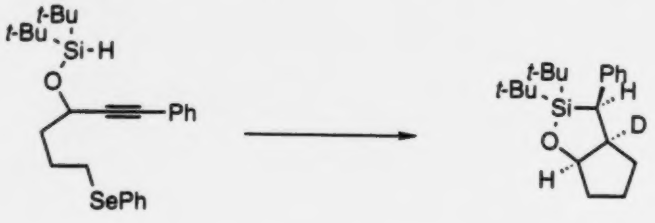
(±)-(3α,3aβ,6β)-2,2-Di-*tert*-butyl-3,3a,4,5,6,6a-hexahydro-3-phenyl-*2H*-cyclopent[*d*][1,2]oxasilole (321).



309 **321**

The general procedure for radical cyclization was followed, using selenide **309** (141.5 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.5 mmol) in PhH (7.5 mL). Refluxing was continued for 0.5 h after the stannane addition. After workup, flash chromatography of the residue over silica gel (1.8 × 14 cm), using increasing amounts of CH_2Cl_2 in hexane (from 5% to 7%), gave an oil that was purified by filtration through a pad of neutral alumina (1.0 × 6 cm), using 1:199 Et_2O–hexane, to give bicyclo **321** (68.5 mg, 72%) as a homogeneous [^1H NMR (400 MHz)], white solid [tlc, silica, 1:4 CH_2Cl_2–hexane]: mp: 49–51 °C; FTIR ($CDCl_3$ cast) 2960, 2938, 2859, 1475, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 9 H), 1.15 (s, 9 H), 1.54–2.03 (m, 6 H), 2.89–3.01 (m, 1 H), 3.40 (d, J = 7.5 Hz, 1 H), 4.48–4.53 (m, 1 H), 7.10–7.15 (m, 1 H), 7.23–7.33 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 21.08 (s'), 22.60 (s'), 24.10 (t'), 28.01 (t'), 28.47 (q'), 28.82 (q'), 35.11 (t'), 36.64 (d'), 47.45 (d'), 83.67 (d'), 124.69 (d'), 128.06 (d'), 129.45 (d'), 142.17 (s'); exact mass *m/z* calcd for $C_{20}H_{32}OSi$ 316.2222, found 316.2220. Anal. Calcd for $C_{20}H_{32}OSi$: C, 75.88; H, 10.19. Found: C, 75.53; H, 10.25.

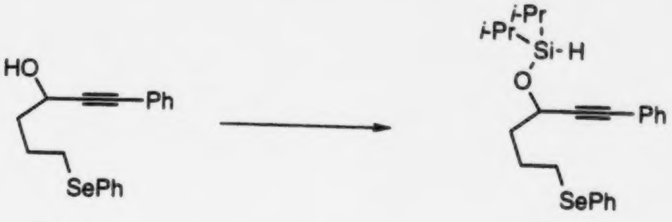
(±)-(3α,3aβ,6β)-2,2-Di-*tert*-butyl-3,3a,4,5,6,6a-hexahydro-3-phenyl-2*H*-[3a-^{2}H$_{1}$]-cyclopent[*d*][1,2]oxasilole (322).



309 **322**

The general procedure for radical cyclization was followed, using selenide **309** (47.2 mg, 0.10 mmol) in PhH (8 mL), Bu_3SnD (39 mg, 1.33 mmol) in PhH (1 mL), and AIBN (3 mg, 0.2 mmol) in PhH. Refluxing was continued for 2 h after the stannane addition. After workup, flash chromatography of the residue over silica gel (1 × 8 cm), using 3:17 CH_2Cl_2–hexane, gave an oil that was purified by filtration through a pad of neutral alumina (0.5 × 3 cm), using hexane (*ca.* 5 mL), to give bicyclo **322** (20.2 mg, 64%) as a homogeneous [^{1}H NMR (400 MHz)], oil: FTIR ($CDCl_3$ cast) 2938, 2857, 1475, 998, 820, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 9 H), 1.14 (s, 9 H), 2.52–2.71 (m, 2 H), 2.72–2.02 (m, 4 H), 3.37 (s, 1 H), 4.47–4.53 (m, 1 H), 7.09–7.16 (m, 1 H), 7.23–7.31 (m, 4 H); ^{2}H NMR ($CHCl_3$, 61.423 MHz) δ 2.68 (s, 1.0 ^{2}H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 21.09 (s'), 22.61 (s'), 24.11 (t'), 27.90 (t'), 28.01* (t'), 28.47 (q'), 28.83 (q'), 35.13 (t'), 36.53 (d'), 36.65* (d'), 47.00 (s, J_{CD} = 20 Hz), 83.63 (d'), 124.69 (d'), 128.07 (d'), 129.47 (d'), 142.18 (s'); exact mass *m/z* calcd for $C_{20}H_{31}DOSi$ 317.2285, found 317.2283. *: Signal from the non deuterated compound (*ca.* 10%).

[3-[1-Phenyl-6-(phenylseleno)-1-hexynyl]oxy]diisopropylsilane (323).

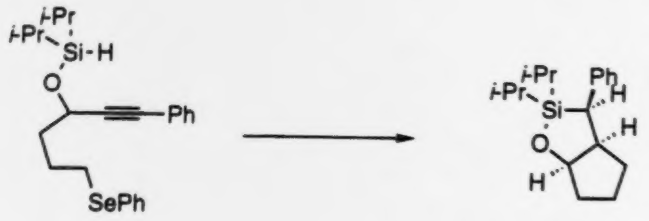


269

323

The general procedure for silylation of alkynols was followed, using alcohol **269** (329.3 mg, 1.00 mmol), imidazole (136.2 mg, 2.00 mmol) in THF (8 mL), and *i*-Pr_2SiHCl (188.1 mg, 1.25 mmol) in THF (1 mL plus 1 mL as a rinse). The mixture was heated for 2.5 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 20 cm), using 1:9 and then 3:17 CH_2Cl_2–hexane, gave silyl ether **323** (397.1 mg, 90%) as a pure [^1H NMR (400 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2942, 2863, 2101, 1089, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98–1.13 (m, 14 H), 1.88–2.02 (m, 4 H), 2.94–3.03 (m, 2 H) 4.269 S, 1 H), 4.60–4.68 (m, 1 H), 7.17–7.27 (m, 3 H), 7.27–7.33 (m, 3 H), 7.33–7.42 (m, 2 H), 7.46–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 12.46 (d'), 12.60 (d'), 17.36 (q'), 17.48 (q'), 17.55 (q'), 25.85 (t'), 27.66 (t'), 37.43 (t'), 65.14 (d'), 85.06 (s'), 89.91 (s'), 122.94 (s'), 126.78 (d'), 128.26 (d'), 129.04 (d'), 130.33 (s'), 131.63 (d'), 132.76 (d'); exact mass *m/z* calcd for $C_{24}H_{32}O^{80}SeSi$ 444.1389, found 444.1404. Anal. Calcd for $C_{24}H_{32}OSeSi$: C, 64.99; H, 7.27. Found: C, 65.18; H, 7.17.

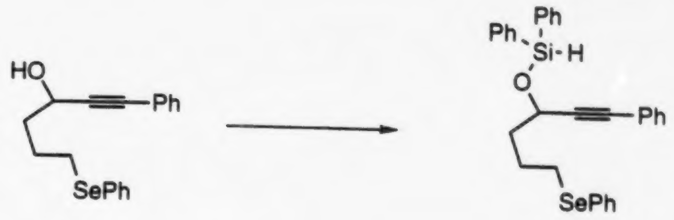
(±)-(3α,3aβ,6β)-3,3a,4,5,6,6a-Hexahydro-2,2-diisopropyl-3-phenyl-*2H*-cyclopent[*d*][1,2]oxasilole (323).



323 **324**

The general procedure for radical cyclization was followed, using selenide **323** (158.9 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.15 mmol) in PhH (7.5 mL). Refluxing was continued for 0.5 h after the stannane addition. After workup, flash chromatography of the residue over silica gel (1.8 × 19 cm), using increasing amounts of CH_2Cl_2 in hexane (from 10% to 40%), gave an oil that was purified by filtration through a pad of neutral alumina (0.5 × 2.5 cm), using hexane (*ca.* 5 mL), to give bicyclo **324** (30.1 mg, 35%) as a pure [^1H NMR (400 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 2959, 2942, 2866, 1495, 1465, 1027, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, $J = 7.0$ Hz, 3 H), 1.06 (d, $J = 7.0$ Hz, 3 H), 1.07 (d, $J = 7.0$ Hz, 3 H), 1.10 (d, $J = 7.0$ Hz, 3 H), 1.13–1.28 (m, 2 H) 1.48–1.68 (m, 2 H), 1.69–1.80 (m, 1 H), 1.81–1.98 (m, 2 H), 1.65–1.75 (m, 1 H), 3.07 (d, $J = 7.0$ Hz, 1 H), 4.46 (td, $J = 4.5$, 1.5 Hz, 1 H), 7.11–7.17 (m, 1 H), 7.21–7.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 12.96 (d'), 14.46 (d'), 17.70 (q'), 17.83 (q'), 17.87 (q'), 17.98 (q'), 24.55 (t'), 28.58 (t'), 34.74 (t'), 35.54 (d'), 49.55 (d'), 83.86 (d'), 124.89 (d'), 128.19 (d'), 129.33 (d'), 141.77 (s'); exact mass *m/z* calcd for $C_{18}H_{28}OSi$ 288.1910, found 288.1908.

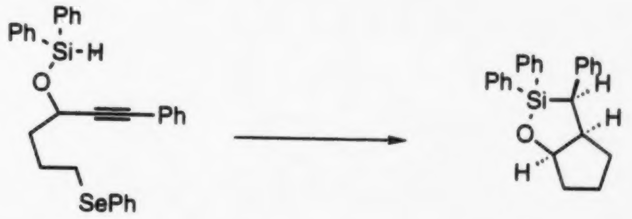
[3-[1-Phenyl-6-(phenylseleno)-1-hexynyl]oxy]diphenylsilane (325).



269 **325**

The general procedure for silylation of alkynols was followed, using alcohol **269** (98.8 mg, 0.30 mmol), imidazole (24.5 mg, 0.36 mmol) in PhH (2.0 mL), and Ph_2SiHCl (72.2 mg, 0.33 mmol) in PhH (0.5 mL plus 0.5 mL as a rinse).[157b] The mixture was heated for 2 h, and cooled to room temperature. The white solid was removed by filtration through glass wool. The clear filtrate containing **325** was used directly for the next step. The interpretation of ^{1}H NMR of a similar experiment, using C_6D_6 as solvent, indicated that the protection reaction was complete (no traces of starting material)

(±)-(3α,3aβ,6β)-3,3a,4,5,6,6a-Hexahydro-2,2,3-triphenyl-*2H*-cyclopent[*d*][1,2]oxasilole (326).

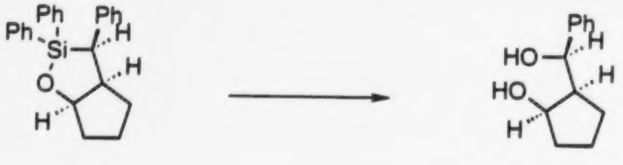


325 **326**

The general procedure for radical cyclization was followed, using crude selenide **325** in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.5 mmol) in PhH. Refluxing was continued for 2 h after the stannane addition. The crude product was used directly for the next step.

Note: Bicyclic compound **326** is stable and can be isolated, but in very low yield because of the difficulty to obtain the compound free of stannane residues.

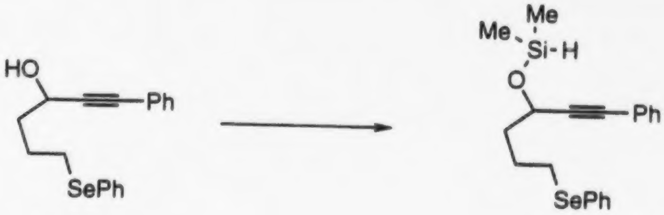
(±)-(1*R**,2*R**,1'*R**)-2-(1-Hydroxy-1-phenylmethyl)-cyclopentanol (330).



326 **330**

H_2O_2 (30% solution in H_2O, 0.70 mL, 6.2 mmol) was added to a stirred mixture of crude **326**, $KHCO_3$ (6 mg, 0.6 mmol) and $KF{\cdot}2H_2O$ (3.5 mg, 0.6 mmol) in a 1:1 mixture of MeOH–THF (12 mL) at room temperature. The mixture was heated at 60 °C overnight, then cooled to room temperature. Water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 9 cm), using increasing amounts of EtOAc in hexane (from 15% to 25%), gave diol **330** (11.0 mg, 14%) as a colorless oil [R_f 0.30, silica, 3:7 EtOAc–hexane]: FTIR ($CDCl_3$ cast) 3345, 2960, 1451, 1031, 999 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43–1.72 (m, 3 H), 1.73–2.10 (m, 4 H), 2.51 (br s, 1 H), 3.48 (br s, 1 H), 4.33 (td, $J = 4.5$, 2.0 Hz, 1 H), 5.17 (d, $J = 3.5$ Hz, 1 H), 7.21–7.29 (m, 1 H), 7.30–7.41 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 21.79 (t'), 21.99 (t'), 36.00 (t'), 51.67 (d'), 73.94 (d'), 76.61 (d'), 125.79 (d'), 127.14 (d'), 128.28 (d'), 144.17 (s'); exact mass *m/z* calcd for $C_{12}H_{14}O$ (M - H_2O)$^+$ 174.1045, found 174.1043; mass (CI) *m/z* calcd for $C_{12}H_{16}O_2$ (M + 18)$^+$ 210, found 210.

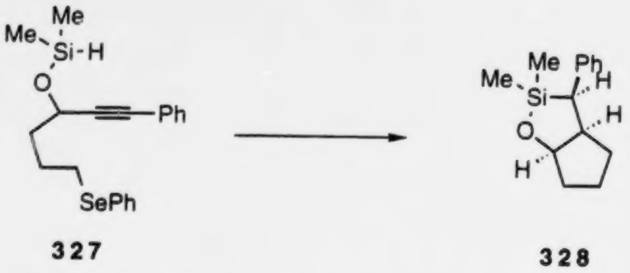
[3-[1-Phenyl-6-(phenylseleno)-1-hexynyl]oxy]dimethylsilane (327).



269 **327**

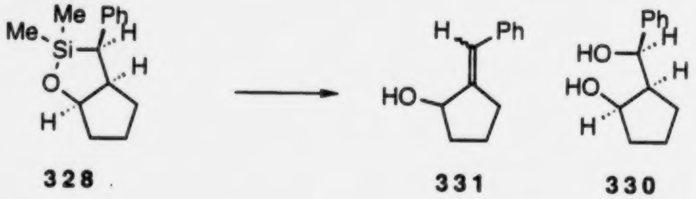
Solid NH_4Cl (ca 1 mg) was added to a homogeneous mixture of $(Me_2SiH)_2NH$ (60 mg, 0.45 mmol) and alcohol **269** (98.8 mg, 0.30 mmol) in a round-bottomed flask equipped with a rubber septum.[154c] The mixture was swirled to distribute the material uniformly over the walls of the flask, and the flask was placed in a desiccator, and allowed to stand at room temperature overnight. The mixture was placed under oil-pump vacuum for 1 h [in order to remove the excess of $(Me_2SiH)_2NH$], and the residual crude **328** was used directly for the next step. A sample from a similar experiment [NH_4Cl (ca 1 mg), $(Me_2SiH)_2NH$ (20.1 mg, 0.15 mmol), alcohol **269** (32.9 mg, 0.10 mmol)] was dissolved in C_6D_6 and filtered through glass wool, to give selenide **327** as a pure [^{1}H NMR, (400 MHz)], colorless oil: FTIR (C_6D_6 cast) 2946, 2123, 1489, 1252, 1086, 1073, 900 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.19 (d, J = 2.8 Hz, 3 H), 0.24 (d, J = 2.8 Hz, 3 H), 1.88–1.93 (m, 4 H), 2.63–2.72 (m, 2 H), 4.51–4.58 (m, 1 H), 4.97–5.04 (m, 1 H), 6.89–7.00 (m, 6 H), 7.34–7.47 (m, 4 H); ^{13}C NMR (C_6D_6, 100 MHz) δ –1.00 (q'), –0.82 (q'), 26.11 (t'), 27.46 (t'), 38.57 (t'), 64.36 (d'), 85.71 (s'), 90.37 (s'), 123.32 (s'), 126.79 (d'), 128.44 (d'), 128.54 (d'), 129.21 (d'), 313.01 (s'), 131.87 (d'), 133.00 (d'); exact mass *m/z* calcd for $C_{20}H_{24}O^{80}SeSi$ 388.0762, found 388.0762.

(±)-(3α,3aβ,6β)-3,3a,4,5,6,6a-hexahydro-2,2-dimethyl-3-phenyl-*2H*-cyclopent[*d*][1,2]oxasilole (328).



The general procedure for radical cyclization was followed, using the crude product from the preceding experiment in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.5 mmol) in PhH (7.5 mL). Refluxing was continued for 2 h after the stannane addition. The crude material was used directly for the next reaction.

2-(Phenylmethylene)cyclopentanol (331) and (±)-(1*R,2*R**,1'*R**)-2-(phenylhydroxymethyl)-cyclopentanol (330).**



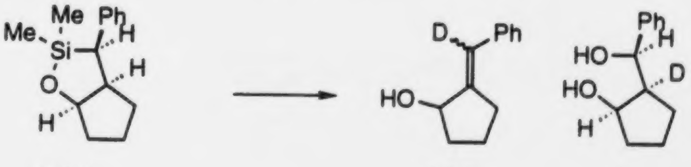
H_2O_2 (30% solution in H_2O, 0.70 mL, 6.2 mmol) was added to a stirred mixture of crude **328**, $KHCO_3$ (6 mg, 0.6 mmol) and $KF{\cdot}2H_2O$ (3.5 mg, 0.6 mmol) in a 1:1 mixture of MeOH–THF (12 mL) at room temperature. The mixture was heated at 60 °C overnight, cooled to room temperature, and aqueous 5% $KHSO_4$ was added (10 mL). Water (was added (10 mL), and the mixture was extracted with EtOAc (3 × 5 mL). the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 10 cm), using increasing amounts of EtOAc in hexane (from 15% to 25%), gave alcohol **331** (15.1 mg, 29%) as a pure [^{1}H NMR (400 MHz)], colorless solid, and diol **330** (15.4 mg, 27%) as a pure [^{1}H NMR (400 MHz)],colorless

oil. Alcohol **331** [R_f 0.45, silica, 3:7 EtOAc–hexane] has: mp: 115–118 °C; FTIR ($CDCl_3$ cast) 3346, 2958, 1491, 1447, 1384, 1200, 1093, 1076, 1029, 753, 694, 517 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.59–1.78 (m, 3 H), 1.89–2.05 (m, 2 H), 2.51–2.62 (m, 1 H), 2.68–2.79 (m, 1 H), 4.55–4.62 (m, 1 H), 6.56–6.61 (m, 1 H), 7.07–7.25 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 22.59 (t'), 29.39 (t'), 34.91 (t'), 77.40 (d'), 123.71 (d'), 126.63 (d'), 128.34 (d'), 128.44 (d'), 137.80 (s'), 147.86 (s'); exact mass *m/z* calcd for $C_{12}H_{14}O$ 174.1045, found 174.1042.

Diol **330** had identical data with diol obtained in the oxidation of bicyclo compound **326**.

The same three reactions were repeated, but using a non aqueous work-up in the last step:[159a] After the oxidation step, the mixture was cooled to 0 °C, and well crushed $Na_2S_2O_4 \cdot 5\ H_2O$ (*ca.* 1 g) was added. The mixture was diluted with Et_2O (20 mL), and filtered through a pad of Celite (3 × 2 cm). The pad was washed with Et_2O (2 × 20 mL), and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1.8 × 8 cm), using increasing amounts of EtOAc in hexane (from 10% to 30%), gave alcohol **331** (23.3 mg, 45%) and diol **330** (19.0 mg, 33%).

2-([1-$^2H_1$]-Phenylmethylene)cyclopentanol (332) and (±)-(1*R**,2*R**,1'*R**)-2-(phenylhydroxymethyl)-[2-$^2H_1$]-cyclopentanol (333).

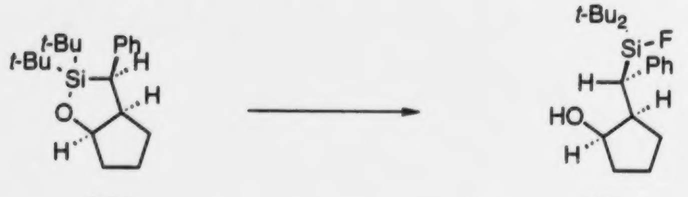


329 **332** **333**

The previous three experiments were performed in the same way, using Bu_3SnD as a reducing agent and an aqueous work-up, to give alcohol **332** (18.8 mg, 38%), and diol **333** (10.2 mg, 18%), both containing some impurities (less than 10%). Alcohol **332** had: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.51–1.80 (m, 3 H), 1.90–2.02 (m, 2 H), 2.54–2.64 (m, 1 H), 2.69–2.80 (m, 1 H), 4.57–4.63 (m, 1 H), 6.55–6.60 (m, *ca.* 0.1 H), 7.19–7.25 (m, 1 H), 7.30–7.40 (m, 4 H): ^{2}H NMR ($CHCl_3$, 61.423 MHz) δ 6.62 (s, 1.0 ^{2}H); exact mass *m/z* calcd for $C_{12}H_{13}DO$ 175.1108, found 175.1110.

Diol **333** had: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42–1.69 (m, 3 H), 1.70–2.02 (m, 3 H), 2.19 (br s, 1 H), 3.16 (br s, 1 H), 4.32–4.37 (m, 1 H), 5.17 (s, 1 H), 7.19–7.25 (m, 1 H), 7.30–7.40 (m, 1 H); ^{2}H NMR ($CHCl_3$, 61.423 MHz) δ 2.06 (s, 1.0 ^{2}H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 21.79 (t'), 21.92 (t'), 36.04 (t'), 73.90 (d'), 76.58 (d'), 125.78 (d'), 127.15 (d'), 128.28 (d'), 144.16 (s'); exact mass *m/z* calcd for $C_{12}H_{13}DO$ $(M - H_2O)^+$ 175.1108, found 175.1109.

(±)(1*R,2*S**)-2-[(1*S*)-1-(di-*tert*-butylfluorosilyl)-1-phenylmethyl]cyclopentanol (334).**

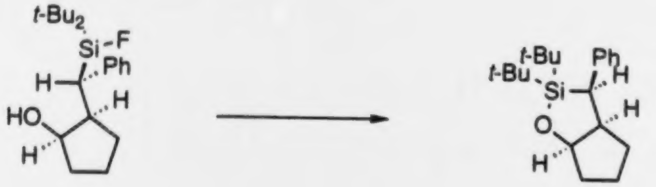


321 **334**

$BF_3{\cdot}Et_2O$ (0.10 mL, 0.81 mmol) was added dropwise to a stirred and cooled (0 °C) solution of bicyclo **321** (72.4 mg, 0.229 mmol) in dry CH_2Cl_2 (2.3 mL), and the mixture was stirred at 0 °C for 7 h.[143] Saturated aqueous $NaHCO_3$ (1 mL) was added, and stirring was continued for 10 min. The cooling bath was then removed, the two layers were separated, and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using increasing amounts of EtOAc in hexane (5% to 10%), gave cyclopentanol **334** (61.7 mg, 80%) as a homogeneous [^{1}H NMR (400 MHz)], white crystals: mp 115–118 °C; FTIR (CH_2Cl_2 cast) 3459, 2939, 2861, 1474, 823, 809, 703, 579 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (d, $J = 0.5$ Hz, 9 H), 1.11 (d, $J_{CF} = 1.0$

Hz, 10 H), 1.50–1.79 (m, 4 H), 1.80–1.96 (m, 1 H), 1.96–2.10 (m, 1 H), 2.38–2.52 (m, 1 H), 2.88 (d, J_{CF} = 12.0 Hz, 1 H), 3.81–3.89 (m, 1 H), 7.11–7.18 (m, 1 H), 7.24–7.36 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 22.12 (s', J_{CF} = 12.2 Hz), 22.67 (t'), 22.75 (s', J_{CF} = 12.6 Hz), 28.36 (q'), 28.82 (q'), 29.39 (t', J = 5.8 Hz), 32.74 (t'), 35.39 (d', J_{CF} = 12.6 Hz), 48.35 (d'), 73.60 (d'), 125.58 (d'), 128.58 (d'), 129.55 (d'), 141.84 (s', J = 5.5 Hz); exact mass *m/z* calcd for $C_{16}H_{33}FSiO$ (M - C_4H_9)$^+$ 279.1581, found 279.1579. Anal. Calcd for $C_{20}H_{33}FOSi$: C, 71.37; H, 9.88. Found: C, 71.37; H, 9.88.

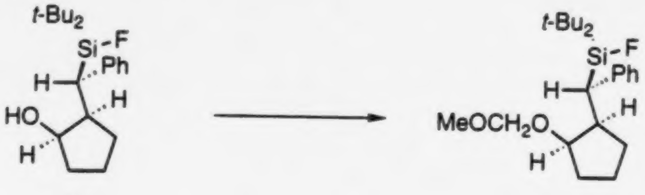
(±)-(3α,3aβ,6β)-2,2-Di-*tert*-butyl-3,3a,4,5,6,6a-hexahydro-3-phenyl-*2H*-cyclopent[*d*][1,2]oxasilole (321).



334 **321**

Anhydrous K_2CO_3 (19.7 mg, 0.14 mmol) was added to a stirred solution of alcohol **334** (47.8 mg, 0.142 mmol) in MeOH (1.4 mL). Stirring was continued for 45 min, and the mixture was evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:99 EtOAc–hexane, gave bicyclo **321** (42.2 mg, 94%) as a pure [^{1}H NMR (400 MHz)], white solid, identical [^{1}H NMR (400 MHz)] to the product obtained from radical cyclization.

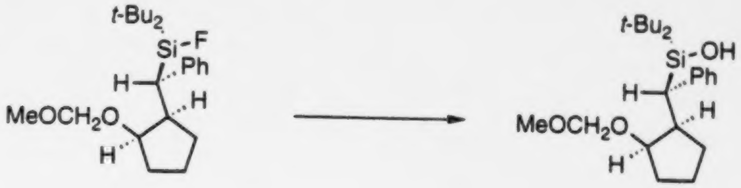
(±)-{(1*R**)-[(1*S**,2*R**)-(2-Methoxymethoxycyclopentyl)phenylmethyl]}di-*tert*-butylfluorosilane (335).



334 **335**

A solution of CH_3OCH_2Cl (23.8 mg, 0.295 mmol) in CH_2Cl_2 (0.5 mL) was added to a stirred solution of alcohol **334** (24.8 mg, 0.074 mmol) and *i*-Pr_2NEt (47.6 mg, 0.37 mmol) in CH_2Cl_2 (3.1 mL). Stirring was continued for 24 h, at which point the reaction was half complete [tlc control, 1:9 silica, EtOAc–hexane]. More reagents [CH_3OCH_2Cl (23.8 mg, 0.295 mmol), *i*-Pr_2NEt (47.6 mg, 0.37 mmol)] and CH_2Cl_2 (3.6 mL)] were then added, and stirring was continued for 24 h. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:99 EtOAc–hexane, gave ether **335** (16.7 mg, 60%) as a pure [^1H NMR (400 MHz)], colorless oil: FTIR (solvent cast) 2939, 2861, 1474, 1448, 1106, 1096, 1046, 824, 809, 704 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 0.97 (s, 9 H), 1.08 (s, 9 H), 1.49–1.70 (m, 3 H), 1.71–1.91 (m, 2 H), 2.10–2.11 (m, 1 H), 2.44–2.55 (m, 1 H), 2.97 (d, J = 12.0 Hz, 1 H), 3.15 (s, 3 H), 3.52–3.57 (m, 1 H), 4.89 (d, J = 6.5 Hz, 1 H), 4.36 (d, J = 6.5 Hz, 1 H), 7.16–7.12 (m, 1 H), 7.18–7.30 (m, 4 H); ^{13}C NMR ($CHCl_3$, 75.469 MHz) δ 20.12 (s', J_{CF} = 12.4 Hz), 22.53 (t', J_{CF} = 1.8 Hz), 22.79 (s', J_{CF} = 12.4 Hz), 28.44 (q'), 28.84 (q'), 29.78 (t', J_{CF} = 6.0 Hz), 31.05 (t'), 35.04 (d', J_{CF} = 12.2 Hz), 48.19 (d'), 55.47 (d'), 80.90 (d'), 96.94 (t'), 125.19 (d'), 128.02 (d'), 129.87 (d'), 142.35 (s', 5.0 Hz); exact mass *m/z* calcd for $C_{20}H_{32}OFSi$ (M - C_2H_5O)$^+$ 335.2204, found 335.2209.

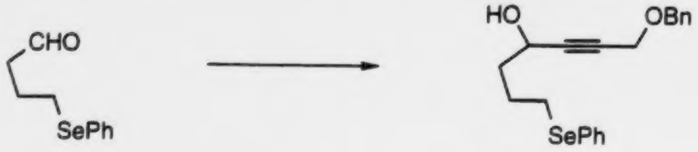
(±)-{(1*R)-[(1*S**,2*R**)-(2-Methoxymethoxycyclopentyl)phenylmethyl]}di-*tert*-butylsilanol (336).**



335 **336**

H_2O_2 (30% solution in H_20, 0.18 mL, 1.6 mmol) was added to a stirred mixture of KF·$2H_2O$ (4.1 mg, 0.043 mmol), K_2CO_3 (6.0 mg, 0.043 mmol), and fluoride **335** (16.5 mg, 0.043 mmol) in 1:1 MeOH–THF (2 mL) at room temperature. The mixture was heated at 65 °C overnight, and then cooled. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 5 cm), using 1:19 EtOAc–hexane, gave silanol **336** (14.3 mg, 87%) as a pure [^{1}H NMR (400 MHz)], yellowish solid: mp 106–111 °C; FTIR (CH_2Cl_2 cast) 3649, 3501, 2937, 2858, 1474, 1044, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 9 H), 1.11 (s, 9 H), 1.56–1.93 (m, 6 H), 2.01–2.11 (m, 1 H), 2.44–2.55 (m, 1 H), 2.87 (d, J = 11.5 Hz, 1 H), 3.11 (s, 3 H), 3.58–3.62 (m, 1 H), 3.78 (d, J = 6.5 Hz, 1 H), 4.30 (d, J = 6.5 Hz, 1 H), 7.03–7.11 (m, 1 H), 7.17–7.27 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 22.06 (s'). 22.63 (t'), 22.96 (s'), 29.06 (q'), 29.20 (q'), 31.04 (t'), 31.06 (t'), 35.84 (d'), 47.54 (d'), 55.34 (q'), 81.02 (d'), 96.85 (t'), 124.86 (d'), 128.20 (d'), 129.51 (d'), 144.21 (s'); exact mass m/z calcd for $C_{20}H_{33}O_2Si$ (M – C_2H_5O)$^+$ 333.2250, found 333.2246; mass (CI) m/z calcd for $C_{22}H_{39}O_3Si$ (M + 1)$^+$ 379, found 379.

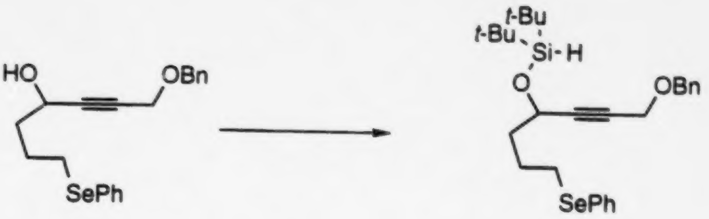
1-(Benzyloxy)-7-(phenylseleno)-2-heptyn-4-ol (340).



267 **340**

The general procedure for addition of an acetylide to an aldehyde was followed, using 3-benzyloxypropyne **318** (R' = CH_2OBn) (351.9 mg, 2.40 mmol) in THF (12 mL), *n*-BuLi (1.41 mL, 1.6 M in hexanes, 2.26 mmol), and an initial reaction period of 15 min aldehyde **267** (340.7 mg, 1.50 mmol) in THF (1.5 mL plus 1.5 mL as a rinse). Stirring was continued for 45 min. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 EtOAc–hexane, gave alcohol **340** (399.3 mg, 71%) as a pure [^1H NMR (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 3409, 3060, 3030, 2939, 2856, 1072, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.78–1.93 (m, 5 H), 2.94 (t, *J* = 7.0 Hz, 2 H), 4.17 (d, *J* = 2.0 Hz, 2 H), 4.39–4.46 (m, 1 H), 4.56 (s, 2 H), 7.20–7.38 (m, 8 H), 7.47–7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 25.78 (t'), 27.44 (t'), 35.75 (t'), 57.40 (t'), 61.97 (d'), 71.76 (t'), 81.16 (s'), 87.23 (s'), 126.80 (d'), 127.95 (d'), 128.13 (d'), 128.50 (d'), 129.08 (d'), 130.21 (s'), 132.67 (d'), 137.37 (s'); exact mass *m/z* calcd for $C_{20}H_{22}O_2{}^{80}SeSi$ 374.0785, found 374.0781. Anal. Calcd for $C_{20}H_{22}O_2SeSi$: C, 64.34; H, 5.94. Found: C, 64.42; H, 5.95.

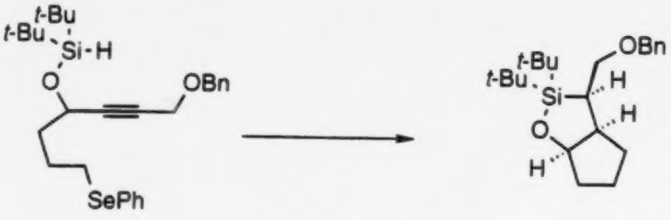
{4-[1-(Benzyloxy)-7-(phenyseleno)-2-heptynyl]oxy}di-*tert*-butylsilane (341).



340 **341**

The general procedure for silylation of alkynols was followed, using alcohol **340** (373.4 mg, 1.00 mmol), imidazole (136.2 mg, 2.00 mmol) in THF (8 mL), and *t*-Bu_2SiHCl (223.5 mg, 1.25 mmol) in THF (1 mL plus 1 mL as a rinse). The mixture was heated for 2.5 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 1:99 and then 1:49 Et_2O–hexane, gave silyl ether **341** (473.0 mg, 92%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2930, 2856, 2093, 1470, 1075, 826 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 9 H), 1.01 (s, 9 H), 1.78–1.98 (m, 4 H), 2.94 (t, J = 7.0 Hz, 2 H), 4.07 (s, 1 H), 4.18 (d, J = 1.5 Hz, 2 H), 4.52–4.59 [m, 3 H, including a s at δ 4.56 (2 H)], 7.19–7.24 (m, 3 H), 7.28–7.36 (m, 5 H), 7.46–7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.82 (s'), 20.10 (s'), 25.64 (t'), 27.31 (q'), 27.34 (q'), 27.71 (t'), 28.30 (t'), 57.36 (t'), 65.80 (t'), 71.39 (t'), 80.97 (s'), 87.22 (s'), 126.79 (d'), 127.86 (d'), 128.16 (d'), 128.45 (d'), 129.04 (d'), 130.34 (s'), 132.72 (d'), 137.58 (s'); exact mass *m/z* calcd for $C_{28}H_{40}O_2{}^{80}SeSi$ 516.1967, found 516.1963. Anal. Calcd for $C_{28}H_{40}O_2SeSi$: C, 65.22; H, 7.82. Found: C, 65.31; H, 8.04.

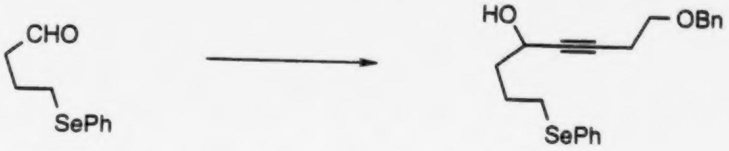
(±)-(3α,3aβ,6β)-2,2-Di-*tert*-butyl-3,3a,4,5,6,6a-hexahydro-3-(benzyloxymethoxy)-*2H*-cyclopent[*d*][1,2]oxasilole (342).



341 **342**

The general procedure for radical cyclization was followed, using selenide **341** (154.7 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.5 mmol) in PhH (7.5 mL). Refluxing was continued for 0.5 h after the stannane addition. After workup, flash chromatography of the residue over silica gel (1.8 × 20 cm), using increasing amounts of CH_2Cl_2 in hexane (from 30% to 45%), gave an oil that was purified by filtration through a pad of neutral alumina (0.5 × 2.5 cm), using hexane (*ca.* 15 mL), to give bicyclo **342** (62.1 mg, 57%) as a homogeneous [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 2934, 2857, 1474, 1031, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 9 H), 1.04 (s, 9 H), 1.37–1.86 (m, 5 H), 2.00–2.12 (m, 1 H), 2.17 (ddd, J = 8.5, 8.5, 8.5 Hz, 1 H), 2.50–2.60 (m, 1 H), 3.77 (d, J = 8.5 Hz, 2 H), 4.47 (ddd, J = 6.0, 6.0, 2.5 Hz, 1 H), 4.51 (d, J = 12 Hz, 1 H), 4.55 (d, J = 12 Hz, 1 H), 7.26–7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.61 (s'), 22.01 (s'), 25.08 (t'), 26.50 (t'), 27.96 (q'), 28.67 (q'), 28.76 (q'), 35.72 (t'), 46.44 (d'), 70.09 (t'), 72.93 (t'), 83.68 (d'), 127.52 (d'), 127.68 (d'), 128.38 (d'), 138.69 (s'); exact mass *m/z* calcd for $C_{18}H_{27}O_2Si$ (M - C_4H_9)$^+$ 303.1780, found 303.1780.

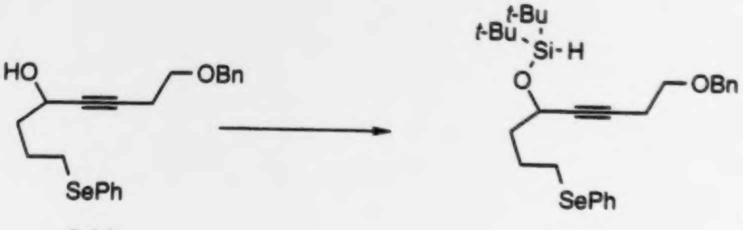
1-(Benzyloxy)-8-(phenylseleno)-3-octyn-5-ol (343).



267 **343**

The general procedure for addition of an acetylide to an aldehyde was followed, using 4-bezyloxybutyne **318** (R' = CH_2CH_2OBn) (384.5 mg, 2.40 mmol) in THF (12 mL), *n*-BuLi (1.41 mL, 1.6 M in hexanes, 2.26 mmol), an initial reaction period of 15 min, and aldehyde **267** (340.7 mg, 1.50 mmol) in THF (1.5.mL plus 1.5 mL as a rinse). Stirring was continued for 45 min. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 EtOAc–hexane, gave alcohol **343** (411.1 mg, 71%) as a pure [^1H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 3412, 2923, 2862, 1074, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.73–1.94 (m, 3 H), 2.48 (td, J = 7.0, 2.0 Hz, 2 H), 2.93 (t, J = 7.0 Hz, 2 H), 3.54 (t, J = 7.0 Hz, 2 H), 4.29–4.38 (m, 1 H), 4.52 (s, 2 H), 7.21–7.38 (m, 8 H), 7.46–7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.13 (t'), 25.79 (t'), 27.52 (t'), 37.86 (t'), 62.08 (d'), 68.34 (t'), 72.97 (t'), 82.05 (s'), 82.49 (s'), 126.78 (d'), 127.72 (d'), 128.46 (d'), 129.03 (d'), 130.33 (s'), 132.63 (d'), 132.70 (d'), 138.06 (s'); exact mass m/z calcd for $C_{21}H_{24}O_2{}^{80}Se$ 388.0942, found 388.0946. Anal. Calcd for $C_{21}H_{24}O_2Se$: C, 65.11; H, 6.24. Found: C, 65.13; H, 6.16.

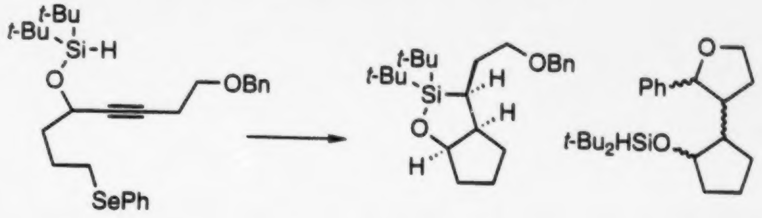
{5-[1-(Benzyloxy)-8-(phenylseleno)-3-octynyl]oxy}di-*tert*-butylsilane (344).



343 **344**

The general procedure for silylation of alkynols was followed, using alcohol **343** (387.4 mg, 1.00 mmol), imidazole (136.2 mg, 2.00 mmol) in THF (8 mL), and *t*-Bu_2SiHCl (223.5 mg, 1.25 mmol) in THF (1 mL plus 1 mL as a rinse). The mixture was heated for 2.5 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 1:99 and then 1:49 Et_2O–hexane, gave silyl ether **344** (502.4 mg, 95%) as a pure [^1H NMR (400 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 2929, 2856, 2093, 1470, 1076, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (s, 9 H), 0.99 (s, 9 H), 1.73–1.82 (m, 2 H), 1.82–1.93 (m, 2 H), 2.49 (td, J = 7.0, 2.0 Hz, 2 H), 2.92 (t, J = 7.5 Hz, 2 H), 3.54 (t, J = 7.0 Hz, 2 H), 4.03 (s, 1 H), 4.41–4.45 (m, 1 H), 4.51 (s, 2 H), 7.20–7.36 (m, 8 H), 7.45–7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.78 (s'), 20.07 (s'), 20.15 (t'), 25.66 (t'), 27.33 (q'), 27.38 (q'), 27.77 (t'), 38.53 (t'), 65.93 (d'), 68.63 (t'), 73.02 (t'), 81.93 (s'), 82.12 (s'), 126.72 (d'), 127.71 (d'), 128.44 (d'), 129.01 (d'), 130.46 (s'), 132.66 (d'), 138.21 (s'); exact mass m/z calcd for $C_{29}H_{42}O_2{}^{80}SeSi$ 530.2119, found 530.2105. Anal. Calcd for $C_{29}H_{42}O_2SeSi$: C, 65.76; H, 7.99. Found: C, 65.72; H, 7.84.

(±)-(3α,3aβ,6β)-2,2-Di-*tert*-butyl-3,3a,4,5,6,6a-hexahydro-3-(2-benzoxyethyl)-*2H*-cyclopent[*d*][1,2]oxasilole (345) and 2-Phenyl-3-oxa-2'[(di-*tert*-butylsilyl)oxy]-1,1'bicyclopentane (354).



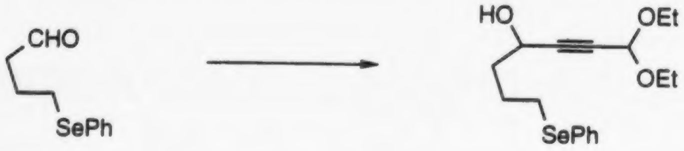
344 **345** **354**

The general procedure for radical cyclization was followed, using selenide **344** (158.9 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.15 mmol) in PhH (7.5 mL). Refluxing was continued for 0.5 h after the stannane addition. After workup, flash chromatography of the residue over silica gel (1.8 × 18 cm), using increasing amounts of CH_2Cl_2 in hexane (from 30% to 40%), gave bicyclopentanes **354** (21.4 mg, 19%) as a mixture of isomers [^{1}H NMR (400 MHz)], and bicyclo compound **345** (63.6 mg, 57%) as a pure [^{1}H NMR (300 MHz)], yellow oil.

Compounds **354** have: FTIR ($CDCl_3$ cast) 2961, 2930, 2856, 2085, 1470, 1056, 825 cm^{-1}; exact mass *m/z* calcd for $C_{23}H_{38}O_2Si$ 374.2641, found 374.2639. The formation of the four inseparable isomers **354** make arduous the assignment of all signals of ^{1}H and ^{13}C NMR.

Compound **345** has: FTIR ($CDCl_3$ cast) 2958, 2934, 2857, 1475, 1112, 1101, 1029, 1016, 1007, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (s, 9 H), 1.06 (s, 9 H), 1.36–1.49 (m, 1 H), 1.50–1.61 (m, 2 H), 1.68–1.84 (m, 3 H), 1.84–2.06 (m, 3 H), 2.31–2.43 (m, 1 H), 3.41–3.50 (m, 1 H), 3.52–3.60 (m, 1 H), 3.38 (ddd, J = 6.0, 6.0, 2.0 Hz, 1 H), 4.47–4.57 (m, 2 H), 7.24–7.31 (m, 1 H), 7.31–7.38 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.73 (s'), 22.08 (s'), 22.80 (d'), 24.76 (t'), 26.45 (t'), 28.08 (q'), 28.31 (t'), 28.67 (q'), 35.68 (t'), 47.17 (d'), 71.59 (t'), 72.97 (t'), 83.54 (d'), 127.55 (d'), 127.22 (d'), 128.39 (d'), 138.63 (s'); exact mass *m/z* calcd for $C_{19}H_{29}O_2Si$ $(M - C_4H_9)^+$ 317.1937, found 317.1934. Anal. Calcd for $C_{23}H_{38}O_2Si$: C, 73.74; H, 10.22. Found: C, 73.69; H, 10.33.

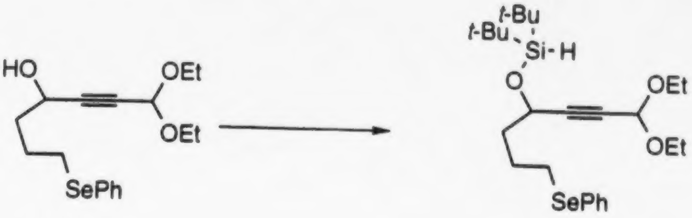
1,1-Diethoxy-7-(phenylseleno)-2-heptyn-4-ol (346).



267 **346**

The general procedure for addition of an acetylide to an aldehyde was followed, using propionaldehyde diethyl acetal **318** (R' = $CH(OEt)_2$) (384 mg, 3.00 mmol) in THF (30 mL), *n*-BuLi (1.41 mL, 1.6 M in hexanes, 2.8 mmol), an initial reaction period of 15 min, and aldehyde **267** (454.2 mg, 2.0 mmol) in THF (5 mL plus 5 mL as a rinse). Stirring was continued for 15 min. Water (80 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 16 cm), using 1:4 EtOAc–hexane, gave alcohol **346** (569.9 mg, 80%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 3427, 2975, 1478, 1437, 1327, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, *J* = 7.0 Hz, 6 H), 1.79–1.95 (m, 5 H), 2.90–2.99 (m, 2 H), 3.51–3.61 (m, 2 H), 3.64–3.77 (m, 2 H), 4.42–4.49 (m, 1 H), 5.27 (d, *J* = 1.5 Hz, 1 H), 7.20–7.29 (m, 3 H), 7.46–7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 15.07 (q'), 25.74 (t'), 27.41 (t'), 37.31 (t'), 60.90 (t'), 60.96 (t'), 61.70 (d'), 80.46 (s'), 86.04 (s'), 91.24 (d'), 126.83 (d'), 129.05 (d'), 130.21 (s'), 132.65 (d'), 132.71 (d'); exact mass *m/z* calcd for $C_{17}H_{24}O_3{}^{80}Se$ 356.0891, found 356.0885. Anal. Calcd for $C_{17}H_{24}O_3Se$: C, 57.46; H, 6.81. Found: C, 57.64; H, 6.83.

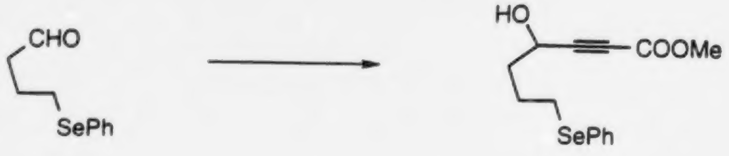
{4-[1,1-Diethoxy-7-(phenylseleno)-2-heptynyl]oxy}di-*tert*-butylsilane (347).



346 **347**

The general procedure for silylation of alkynols was followed, using alcohol **346** (509.8 mg, 1.43 mmol), imidazole (195 mg, 2.86 mmol) in THF (10 mL), and t-Bu_2SiHCl (308 mg, 1.72 mmol) in THF (2 mL plus 2 mL as a rinse). The mixture was heated for 2 h. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 1:19 Et_2O–hexane, gave silyl ether **347** (663.7 mg, 93%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 2930, 2857, 2093, 1470, 1054, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 9 H), 1.00 (s, 9 H), 1.21 (t, J = 7.0 Hz, 6 H), 1.80–1.96 (m, 4 H), 2.93 (t, J = 7.0 Hz, 2 H), 3.50–3.60 (m, 2 H), 3.55–3.65 (m, 2 H), 4.06 (s, 1 H), 4.71–4.77 (m, 1 H), 5.26 (d, J = 1.5 Hz, 1 H), 7.19–7.28 (m 3 H), 7.46–7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 15.10 (q'), 19.76 (s'), 20.11 (s'), 25.56 (t'), 27.27 (q'), 27.32 (q'), 27.69 (t'), 37.18 (t'), 60.83 (t'), 60.89 (t'), 65.61 (d'), 85.60 (s'), 91.41 (d'), 126.78 (d'), 129.04 (d'), 130.35 (s'), 132.72 (d'); exact mass m/z calcd for $C_{21}H_{33}O_3{}^{80}SeSi$ (M - C_4H_9)$^+$ 441.1364, found 441.1365. Anal. Calcd for $C_{25}H_{42}O_3SeSi$: C, 60.34; H, 8.51. Found: C, 60.59; H, 8.66.

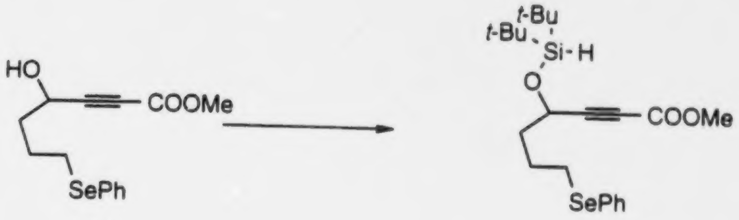
Methyl 4-hydroxy-7-(phenylseleno)-2-heptynoate (349).



267 **349**

n-BuLi (1.83 mL, 1.6 M in hexanes, 2.93 mmol) was added dropwise over *ca.* 5 min to a stirred and cooled (–78 °C) solution of freshly distilled $(Me_3Si)_2NH$ (497.0 mg, 3.08 mmol) in dry THF (15 mL). The cooling bath was removed, and stirring was continued for 30 min. The mixture was then added by cannula to a stirred and cooled (–78 °C) solution of methyl propiolate **318** (R' = CO_2Me) (267 mg, 3.18 mmol) in dry THF (20 mL). Stirring was continued at -78 °C for 30 min, and a solution of aldehyde **267** (454.3 mg, 2.00 mmol) in THF (2.5 mL plus 2.5 mL as a rinse) was injected over *ca.* 5 min. Stirring was continued at -78 °C for 1 h, and saturated aqueous NH_4Cl (10 mL) was added. The cooling bath was removed, and the mixture was allowed to reach room temperature. Water (100 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 × 20 cm), using 1:4 EtOAc–hexane, gave alcohol **349** (537.5 mg, 86%) as a pure [^{1}H NMR (300 MHz)], yellow oil: FTIR ($CHCl_3$ cast) 3416, 2949, 2236, 1716, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82–1.94 (m, 4 H), 2.12–2.19 (m, 1 H), 2.89–2.98 (m, 2 H), 3.78 (s, 3 H), 4.46–4.53 (m, 1 H), 7.21–7.30 (m, 3 H), 7.46–7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 25.45 (t'), 27.27 (t'), 36.60 (t'), 52.66 (q'), 61.58 (d'), 76.52 (s'), 87.66 (s'), 126.98 (d'), 129.17 (d'), 129.94 (s'), 132.83 (d'), 153.73 (s'); exact mass *m/z* calcd for $C_{14}H_{16}O_3{}^{80}SeSi$ 312.0265, found 312.0262. Anal. Calcd for $C_{14}H_{16}O_3SeSi$: C, 54.03; H, 5.18. Found: C, 54.21; H, 5.25.

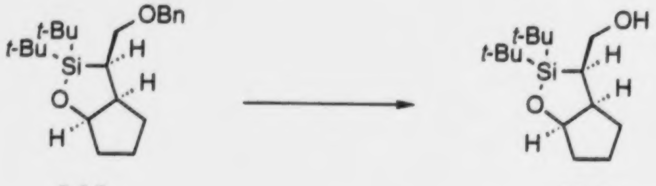
Methyl 4-[(di-*tert*-butylsilyl)oxy]-7-(phenylseleno)-2-hetpynoate (350).



349 **350**

The general procedure for silylation of alkynols was followed, using alcohol **349** (311.2 mg, 1.00 mmol), imidazole (136.2 mg, 2.00 mmol) in THF (8 mL), and *t*-Bu_2SiHCl (223.5 mg, 1.25 mmol) in THF (1 mL plus 1 mL as a rinse). The mixture was heated for 2.5 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 1:50 EtOAc–hexane, gave silyl ether **350** (383.1 mg, 84%) as a pure [^1H NMR (400 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2931, 2858, 2237, 2096, 1716, 1093, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 9 H), 1.01 (s, 9 H), 1.86–1.94 (m, 4 H), 2.91–2.98 (m, 2 H), 3.77 (s, 3 H), 4.06 (s, 1 H), 4.56–4.63 (m 1 H), 7.22–7.28 (m, 3 H), 7.47–7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.77 (s'), 20.11 (s'), 25.28 (t'), 27.19 (q'), 27.23 (q'), 27.54 (t'), 37.44 (t'), 52.91 (q'), 65.48 (q'), 87.72 (s'), 126.91 (d'), 129.08 (d'), 130.07 (s'), 132.90 (d'), 153.81 (s'), one of the signals may be obscured by $CDCl_3$ signals; exact mass *m/z* calcd for $C_{22}H_{34}O_3{}^{80}SeSi$ 454.1443, found 454.1442. Anal. Calcd for $C_{22}H_{34}O_3SeSi$: C, 58.26; H, 7.56. Found: C, 58.42; H, 7.86.

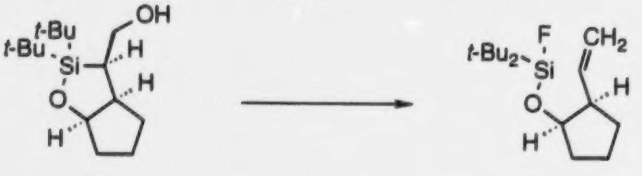
(±)-(3α,3aβ,6β)-2,2-Di-*tert*-butyl-3,3a,4,5,6,6a-hexahydro-2,2-di-*tert*-butyl-3-hydroxymethyl-*2H*-cyclopent[*d*][1,2]oxasilole(360).



342 **360**

Benzyl ether **342** (40.7 mg, 0.113 mmol) in 98% EtOH (1.1 mL) was shaken with Pd/C (5–10%, 40.7 mg), under H_2 at 50 psi in a Parr shaker for 3 h.[166] The mixture was evaporated, and flash chromatography of the residue over silica gel (1 × 10 cm), using 1:9 EtOAc–hexane, gave alcohol **360** (28.9 mg, 95%) as a homogeneous [^{1}H NMR (400 MHz)], white solid: mp 64.5–66 °C; FTIR ($CDCl_3$ cast) 3388, 2960, 2934, 2859, 1474, 1030, 1004, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 1.05 (s, 9 H), 1.39–1.65 (m, 3 H), 1.65–1.78 (m, 2 H), 1.78–1.89 (m, 1 H), 2.01–2.11 (m, 2 H), 2.50–2.60 (m, 1 H), 3.97 (s, 1 H), 3.97–4.02 (m, 1 H), 4.49 (ddd, *J* = 6.0, 6.0, 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.56 (s'), 21.95 (s'), 25.05 (t'), 26.22 (t'), 27.94 (q'), 28.63 (q'), 31.93 (d'), 35.60 (t'), 45.95 (d'), 62.29 (t'), 83.76 (d'); exact mass *m/z* calcd for $C_{11}H_{21}O_2Si$ (M – C_4H_9)$^+$ 213.1311, found 213.1307. Anal. Calcd for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.85; H, 11.27.

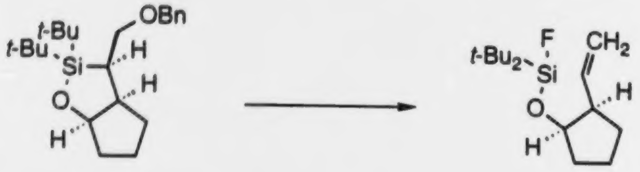
(±)-(1*R**,2*R**)-Di-*tert*-butylfluoro-[(2-vinylcyclopentyl)oxy]silane (361).



360 **361**

BF_3.Et2O (0.10 mL, 0.8 mmol) was added to a stirred and cooled (0 °C) solution of alcohol **360** (27.4 mg, 0.10 mmol) in dry CH_2Cl_2 (2.5 mL).[159b] Stirring at 0 °C was continued for 1 h, saturated aqueous $NaHCO_3$ (1 mL) was added, and the cooling bath was removed. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 5 cm), using hexane, gave fluorosilane **361** (19.9 mg, 77%) as acolorless oil: FTIR ($CDCl_3$ cast) 2966, 2935, 2862, 1473, 1137, 1066, 842, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (d, $J = 0.5$ Hz, 9 H), 1.04 (d, $J = 0.5$ Hz, 9 H), 1.55–1.92 (m, 6 H), 2.37 (dddd, $J = 9.0, 9.0, 9.0, 4.0$ Hz, 1 H), 4.48–4.53 (m, 1 H), 4.99–5.09 (m, 2 H), 5.99 (ddd, $J = 17.5, 10.0, 8.0$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.08 (s', $J_{CF} = 14.5$ Hz), 20.70 (s', $J_{CF} = 16.0$ Hz), 21.78 (t'), 27.04 (s'), 27.24 (s'), 28.85 (t'), 35.28 (t'), 50.58 (d'), 78.63 (d'), 114.76 (s'), 139.32 (d'); exact mass m/z calcd for $C_{11}H_{20}FOSi$ (M - C_4H_9) 215.1267, found 215.1267.

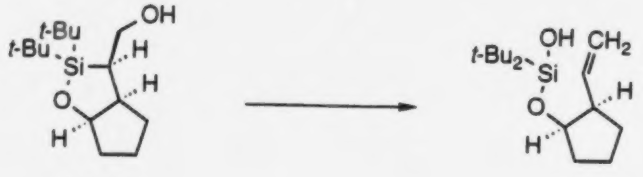
(±)-(1*R**,2*R**)-Di-*tert*-butylfluoro-[(2-vinylcyclopentyl)oxy]silane (361).



342 **361**

$BF_3{\cdot}Et_2O$ (0.10 mL, 0.8 mmol) was added to a stirred and cooled (0 °C) solution of benzyl ether **342** (23.8 mg, 0.066 mmol) in dry CH_2Cl_2 (2.5 mL).[159b] Stirring at 0 °C was continued for 1 h, saturated aqueous $NaHCO_3$ (1 mL) was added, and the cooling bath was removed. The mixture was stirred for 15 min, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 5 cm), using hexane, gave fluorosilane **361** (11.6 mg, 69%) as a colorless oil, whose ^1H NMR spectrum was identical to that of the preceding method.

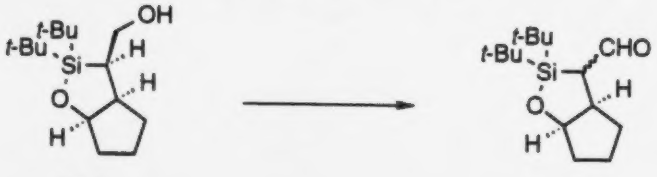
(±)-(1*R**,2*R**)-Di-*tert*-butyl-[(2-vinylcyclopentyl)oxy]silanol (362).



360 **362**

Crystalline alcohol **360** (13.5 mg, 0.050 mmol) was added to a stirred mixture of *t*-BuOK (8.8 mg, 0.075 mmol) in dry THF (1 mL). Stirring was continued at room temperature for 10 min, and saturated aqueous NH_4Cl (*ca.* 5 drops) and water (2 mL) were added sequentially. The mixture was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated, to give pure [^1H NMR, (400 MHz)] alcohol **362** (11.2 mg, 83%) as a colorless oil: FTIR ($CHCl_3$ cast) 3492, 2965, 2934, 2859, 1473, 1136, 1056, 911, 828 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 18 H), 1.53–1.91 (m, 7 H), 2.36 (dddd, J = 9.0, 9.0, 9.0, 4.0 Hz, 1 H), 4.41–4.46 (m, 1 H), 5.00–5.09 (m, 2 H), 6.01 (ddd, J = 17.5, 10.0, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.46 (s'), 20.84 (s'), 21.92 (t'), 27.66 (q'), 27.76 (q'), 28.91 (t'), 50.65 (d'), 77.75 (d'), 114.75 (t'), 140.23 (d'); exact mass *m/z* calcd for $C_{18}H_{27}O_2Si$ $(M - C_4H_9)^+$ 303.1780, found 303.1782.

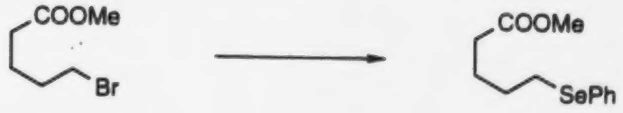
(±)-(3α,3aβ,6β)-2,2-Di-*tert*-butyl-3,3a,4,5,6,6a-hexahydro-3-phenyl-*2H*-cyclopent[*d*][1,2]oxasilole carboxaldehyde (355).



360 **355**

Dry DMSO (0.17 mL, 2.2 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.10 ml, 1.1 mmol) in dry CH_2Cl_2 (3.5 mL).[168] Stirring was continued for 15 min, and a portion of this solution (*ca.* 0.3 mL) was quickly withdrawn into a syringe and transferred to a stirred and cooled (-78 °C) solution of alcohol **360** (18.5 mg, 0.068 mmol) in dry CH_2Cl_2 (1 mL). Stirring was continued at -78 °C for 15 min, and dry Et_3N (0.1 mL) was added. Stirred was continued at -78 °C for 5 min, the cooling bath was removed, and the mixture was allowed to reach room temperature. Water (1 mL) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.0 × 5 cm), using 1:9 EtOAc–hexane, gave aldehyde **355** (12.4 mg, 67%) as a slightly impure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 2936, 2860, 1692, 1474, 1069, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 9 H), 1.09 (s, 9 H), 1.29–2.13 (m, 6 H), 3.03 (dd, J = 8.0, 3.5 Hz, 1 H), 4.53 (ddd, J = 6.0, 6.0, 2.5 Hz, 1 H), 9.92 (d, J = 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.75 (s'), 22.48 (s'), 25.68 (t'), 27.66 (q'), 27.83 (t'), 28.34 (q'), 34.74 (t'), 45.52 (d'), 47.17 (d'), 84.37 (d'), 203.64 (d'); exact mass *m/z* calcd for $C_{15}H_{28}O_2Si$ 268.1859, found 268.1854.

Methyl 7-(phenylseleno)-pentanoate (364).

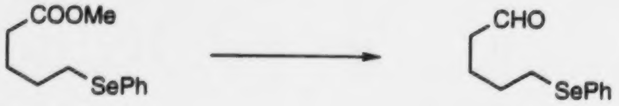


363 **364**

NaBH$_4$ (2.13 g, 56.3 mmol) was added in 10 portions over *ca.* 10 min to a stirred suspension of PhSeSePh (8.37 g, 26.7 mmol) in absolute EtOH (170 mL). (The mixture became faintly yellow, and the internal temperature rose to *ca.* 50 °C.) A solution of bromo ester[109a] **363** in absolute EtOH (20 mL plus 10 mL as a rinse) was then added, and the mixture was heated at 78 °C for 2 h, cooled, and filtered. The filtrate was concentrated to *ca.* 30 mL, and diluted with Et_2O (350 mL). The organic layer was washed with water (2 × 250 mL), dried (Na_2SO_4), and evaporated to give crude **364** (13.9659 g, 96.4 % over two steps) as a reddish oil. Flash chromatography of a small sample over silica gel, using

1:24 EtOAc–hexane, gave pure **364** as a slightly yellow oil: FTIR ($CDCl_3$ cast) 2948, 1737, 1579, 1478, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.67–1.84 (m, 4 H), 2.34 (t, J = 7.0 Hz, 2 H), 2.92 (t, J = 7.0 Hz, 2 H), 3.67 (s, 3 H), 7.21–7.33 (m, 3 H), 7.45–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.05 (t'), 27.31 (t'), 29.57 (t'), 33.48 (t'), 51.52 (q'), 126.80 (d'), 129.04 (d'), 130.27 (s'), 132.61 (d'), 173.75(s'); exact mass *m/z* calcd for $C_{12}H_{16}O_2{}^{80}Se$ 272.0315, found 272.0317.

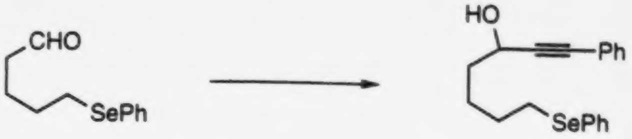
7-(Phenylseleno)-1-pentanal (365).



364 **365**

DIBAL–H^{200} (10.0 mL, 10.0 mL, 1 M in CH_2Cl_2, 10.0 mmol) was injected dropwise over *ca.* 10 min to a stirred and cooled (–78 °C) solution of crude ester **364** (2.71 g, 10.0 mmol) in dry CH_2Cl_2 (100 mL). The solution was stirred for 30 min, and $Na_2SO_4 \cdot 10\ H_2O$ (3.22 g, 10.0 mmol) was added. The cooling bath and Ar inlet were removed, the mixture was stirred for 1 h, and then dried by addition of anhydrous Na_2SO_4 (9.5 g). Stirring was continued for 30 min, and the mixture was filtered. The solids were washed with CH_2Cl_2 (2 × 100 mL), and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm), using 2:25 EtOAc–hexane, gave aldehyde **365** (2.1034 g, 87.3%) as pure [^1H NMR (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2931, 1722, 1478, 1437, 736, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.68–1.82 (m, 4 H), 2.40–2.47 (m, 2 H), 2.88–2.97 (m, 2 H), 7.21–7.31 (m, 3 H), 7.45–7.53 (m, 2 H), 9.57 (t, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 22.12 (t'), 27.36 (t'), 29.54 (t'), 43.23 (t'), 126.87 (d'), 129.06 (d'), 130.14 (s'), 132.65 (d'), 202.00 (d'); exact mass *m/z* calcd for $C_{11}H_{14}O^{80}Se$ 242.0210, found 242.0207.

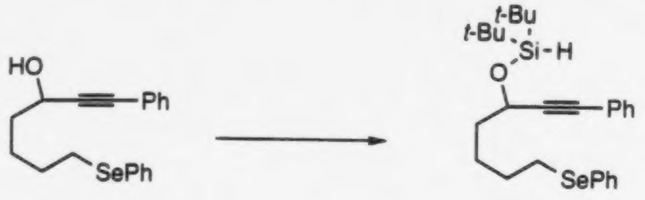
1-Phenyl-7-(phenylseleno)-1-heptyn-3-ol (366).



365 **366**

The general procedure for addition of an acetylide to an aldehyde was followed, using phenylacetylene **268** (690 mg, 6.74 mmol) in THF (20 mL), *n*-BuLi (3.70 mL, 1.6 M in hexanes, 5.92 mmol), an initial reaction period of 5 min, and aldehyde **365** (1 206 mg, 5.00 mmol) in THF (8.0 mL plus 2.0 mL as a rinse). Stirring was continued for 15 min. Water (100 mL) was added, and the mixture was extracted with $CHCl_3$ (1 × 100 mL, 2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 × 13 cm), using 1:9 EtOAc–hexane, gave alcohol **366** (1295 mg, 75.4%) as a pure [^1H NMR (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 3391, 2934, 2859, 1578, 1488, 1477, 1436, 756, 735, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60–1.47 (m, 2 H), 1.74–1.88 (m, 4 H), 1.97 (d, $J = 4.5$ Hz, 1 H), 2.95 (t, $J = 7.5$ Hz, 2 H), 4.56–4.66 (m, 1 H), 7.20–7.29 (m, 3 H), 7.29–7.36 (m, 3 H), 7.40–7.47 (m, 2 H), 7.47–7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.44 (t'), 27.72 (t'), 29.83 (t'), 37.25 (t'), 62.78 (d'), 85.07 (s'), 89.94 (s'), 122.58 (s'), 126.75 (d'), 128.31 (d'), 128.44 (d'), 129.03 (d'), 130.42 (s'), 131.71 (d'), 132.60 (d'); exact mass *m/z* calcd for $C_{19}H_{20}OSe$ 344.0679, found 344.0681.

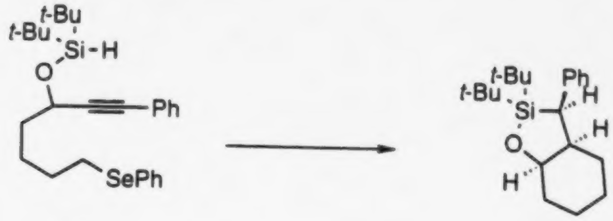
{3-[1-Phenyl-7-(phenylseleno)-1-heptynyl]oxy}di-*tert*-butylsilane (367).



366 **367**

The general procedure for silylation of alkynols was followed, using alcohol **366** (307.4 mg, 0.895 mmol), imidazole (121.9 mg, 1.79 mmol), and *t*-Bu_2SiHCl (200.0 mg, 1.12 mmol) in dry THF (1.0 mL plus 1.0 mL as a rinse). The mixture was heated for 2.5 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 20 cm), using increasing amounts of CH_2Cl_2 in hexane (from 4% to 6%), gave silyl ether **367** (344.2 mg, 79%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 2930, 2856, 2097, 1470, 1087, 825 cm^{-1}; ^{1}H NMR ($CHCl_3$, 300 MHz) δ 1.02 (s, 9 H), 1.06 (s, 9 H), 1.61–1.72 (m, 2 H), 1.72–1.86 (m, 4 H), 2.96 (t, J = 7.5 Hz, 2 H), 4.14 (s, 1 H), 4.67 (t, J = 6.0 Hz, 1 H), 7.20–7.27 (m, 3 H), 7.27–7.33 (m, 3 H), 7.33–7.46 (m, 2 H), 7.46–7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.85 (s'), 20.17 (s'), 25.40 (t'), 27.37 (q'), 27.40 (q'), 27.84 (t'), 30.03 (t'), 37.90 (t'), 66.58 (d'), 84.99 (s'), 90.27 (s'), 123.15 (s'), 126.70 (d'), 128.13 (d'), 128.26 (d'), 129.02 (d'), 130.58 (s'), 131.59 (d'), 132.57 (d'); exact mass *m/z* calcd for $C_{27}H_{38}O^{80}SeSi$ 486.1858, found 486.1860. Anal. Calcd for $C_{27}H_{38}OSeSi$: C, 66.78; H, 7.89. Found: C, 66.84; H, 8.11.

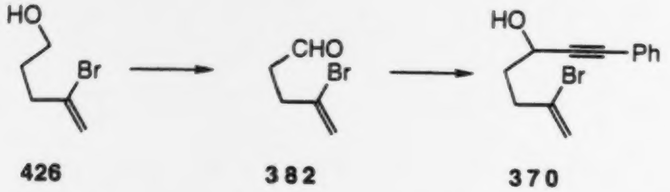
(±)-(3α,3aβ,6β)-Octahydro-2,2-di-*tert*-butyl-3-phenylbenz[*d*][1,2]oxasilole (368).



367 **368**

The general procedure for radical cyclization was followed, using selenide **367** (145.7 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.5 mmol) in PhH (7.5 mL). Refluxing was continued for 0.5 h after the stannane addition. After workup, flash chromatography of the residue over silica gel (1.8 × 20 cm), using increasing amounts of CH_2Cl_2 in hexane (from 5% to 20%), gave an oil that was purified by filtration through a pad of neutral alumina (1.0 × 5 cm), using hexane (*ca.* 10 mL), to give bicyclo **368** (24.6 mg, 24%) as a homogeneous [^{1}H NMR (300 MHz), tlc, silica, 1:4 CH_2Cl_2–hexane], white solid: mp 111–112.5 °C; FTIR ($CHCl_3$ cast) 2934, 2858, 1496, 977 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (s, 9 H), 1.19 (s, 9 H), 1.37–1.59 (m, 5 H), 1.62–1.72 (m, 1 H), 2.09–2.17 (m, 2 H), 2.28–2.40 (m, 1 H), 3.20 (d, J = 6.5 Hz, 1 H), 4.13–4.18 (m, 1 H), 7.10–7.18 (m, 1 H), 7.22–7.29 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.20 (t'), 21.40 (s'), 23.15 (s'), 24.98 (t'), 25.43 (t'), 28.98 (q'), 29.84 (q'), 31.81 (t'), 40.83 (d'), 43.60 (d'), 75.62 (d'), 125.05 (d'), 128.02 (d'), 130.72 (d'), 140.62 (s'); exact mass *m/z* calcd for $C_{21}H_{34}OSi$ 330.2379, found 330.2378. Anal. Calcd for $C_{21}H_{34}OSi$: C, 76.30; H, 10.37. Found: C, 76.19; H, 10.20.

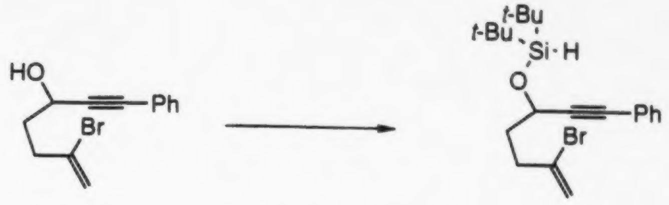
6-Bromo-1-phenyl-6-hepten-1-yn-3-ol (370).



PCC (1.62 g, 7.50 mmol) was tipped into a stirred solution of alcohol **426** (825 mg, 5.00 mmol) in dry CH_2Cl_2 (50 mL). Stirring was continued for 1.5 h. Anhydrous Et_2O (50 mL) was added, and the mixture were filtered through a pad of Florisil (2 × 6 cm). The pad was washed with Et_2O (3 × 25 mL), and the combined filtrates were evaporated to give crude aldehyde **382**, which was used directly for the next step.

The general procedure for addition of an acetylide to an aldehyde was followed, using phenylacetylene **268** (511 mg, 5.00 mmol) in THF (35 mL), *n*-BuLi (3.1 mL, 1.6 M in hexanes, 5.0 mmol), an initial reaction period of 15 minutes, and aldehyde **382** in THF (2.5 mL plus 2.5 mL as a rinse). Stirring was continued for 45 minutes. Water (200 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 16 cm), using 1:4 EtOAc–hexane, gave the alcohol **370** (705.6 mg, 53% over two steps) as a yellowish oil, containing slight impurities [^{1}H NMR (400 MHz)], but suitable for the silylation step. The material had: FTIR ($CHCl_3$ cast) 3341, 1629, 1490, 1050, 889 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.99 (br s, 1 H), 2.03–2.13 (m, 2 H), 2.66–2.72 (m, 2 H), 4.65 (t, $J = 6.5$ Hz, 1 H), 5.44 (d, $J = 1.5$ Hz, 1 H), 5.64–5.67 (m, 1 H), 7.27–7.37 (m, 3 H), 7.40–7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 35.99 (t'), 37.28 (t'), 61.66 (d'), 85.51 (s'), 89.27 (s'), 117.38 (t'), 122.39 (s'), 128.36 (d'), 128.59 (d'), 131.73 (d'), 133.36 (s'); exact mass *m/z* calcd for $C_{13}H_{13}O^{81}Br$ 266.0129, found 266.0126. Anal. Calcd for $C_{13}H_{13}OBr$: C, 58.89; H, 4.94; Br, 30.14. Found: C, 58.93; H, 4.82; Br, 30.03.

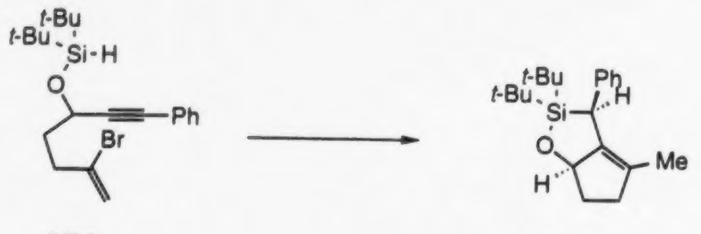
{3-[6-Bromo-1-phenyl-6-hepten-1-ynyl]oxy}di-*tert*-butylsilane (371).



370 **371**

The general procedure for silylation of alkynols was followed, using alcohol **370** (530.3 mg, 2.00 mmol), imidazole (272 mg, 4.00 mmol) in THF (18 mL), and *t*-Bu_2SiHCl (429 mg, 2.40 mmol) in THF (1 mL plus 1 mL as a rinse). The mixture was heated for 2.5 h. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 3:97 CH_2Cl_2–hexane, gave silyl ether **371** (716.8 mg, 88%) as a pure [^{1}H NMR (300 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2930, 2857, 2098, 1086, 826 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (s, 9 H), 1.06 (s, 9 H), 2.03–2.10 (m, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 4.16 (s, 1 H), 4.73 (t, J = 6.0 Hz, 1 H), 5.43 (d, J = 1.5 Hz, 1 H), 5.62–5.66 (m, 1 H), 7.27–7.34 (m, 3 H), 7.37–7.46 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.85 (s'), 20.20 (s'), 27.36 (q'), 27.40 (q'), 36.81 (t'), 37.16 (t'), 65.45 (d'), 85.49 (s'), 89.49 (s'), 117.01 (t'), 122.96 (s'), 128.32 (d'), 131.62 (d'), 133.94 (s'); exact mass *m/z* calcd for $C_{17}H_{22}O^{81}BrSi$ (M - C_4H_9)$^+$ 351.0603, found 351.0606. Anal. Calcd for $C_{21}H_{31}OBrSi$: C, 61.90; H, 7.67; Br, 19.61. Found: C, 62.03; H, 7.67; Br, 19.71.

(±)-(3α,6β)-2,2-Di-*tert*-butyl-3,5,6,6a-tetrahydro-4-methyl-butyl-3-phenyl-2*H*-cyclopent[*d*][1,2]oxasilole (372).

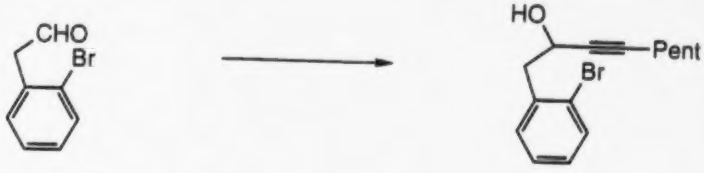


371 **372**

The general procedure for radical cyclization was followed, using bromide **371** (122.2 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.15 mmol) in PhH (7.5 mL). Refluxing was continued for 30 min. after the stannane addition. After work up, flash chromatography of the residue over silica gel (1.8 × 17 cm), using increasing amounts of CH_2Cl_2 in hexane (from 10% to 40%), gave an oil that was purified by filtration through a pad of neutral alumina (0.5 × 2.5 cm), using hexane (*ca.* 10 mL), to give bicyclo **372** (45.1 mg, 46%) as a mixture (3:7) of inseparable isomers [R_f 0.12, silica, CH_2Cl_2–hexane (1:4)]: FTIR ($CDCl_3$ cast) 2959, 2933, 2858, 1471, 1053, 861, 823, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 2.7 H), 0.84 (s, 6.3 H), 1.08 (s, 0.27 H), 1.15 (s, 6.3 H), 1.43 (s, 2.1 H), 1.62 (s, 0.9 H), 1.64–1.81 (m, 1.2 H), 2.30–2.43 (m, 2.2 H), 2.44–2.66 (m, 0.6 H), 3.46–3.51 (m, 0.3 H), 3.67–3.73 (m, 0.7 H), 7.92–5.02 (m, 0.7 H), 5.28–5.35 (m, 0.3 H), 7.04–7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 14.62* (q'), 16.37 (q'), 21.03* (s'), 21.82 (s'), 22.58 (s'), 22.84* (s'), 28.00 (q'), 28.10* (q'), 28.68 (q'), 31.27* (d'), 33.46 (t'), 34.20 (d'), 34.30* (t'), 37.22* (t'), 37.82 (t'), 88.05 (d'), 88.56* (d'), 124.33* (d'), 124.55 (d'), 127.54* (d'), 127.71 (d'), 128.15* (d'), 129.24 (s'), 129.47 (d'), 135.89* (s'), 138.99* (s'), 139.60 (s'), 140.30* (s'); exact mass *m/z* calcd for $C_{21}H_{32}OSi$ 328.2222, found 328.2222.

* Belongs to the minor isomer.

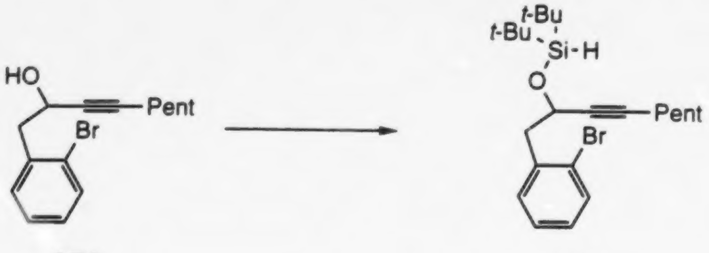
1-(2-Bromophenyl)-3-nonyn-1-ol (383).



383 **373**

The general procedure for addition of an acetylide to an aldehyde was followed, using 1-heptyne **318** (R' = *n*-C_5H_{11}) (360.6 mg, 3.70 mmol) in THF (12.5 mL), *n*-BuLi (2.19 mL, 1.6 M in hexanes, 3.50 mmol), an initial reaction period of 15 min, and (2-bromophenyl)acetaldehyde[171] **383** (398.1 mg, 2.00 mmol) in THF (2.5 mL plus 2.5 mL as a rinse). Stirring was continued for 30 min. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 18 cm), using increasing amounts of EtOAc in hexane (from 5% to 10%), gave alcohol **373** (382.9 mg, 65%) as a pure [^{1}H NMR (400 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 3355, 2931, 1471, 1440, 1024, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85–0.95 (m, 3 H), 1.26–1.38 (m, 4 H), 1.44–1.54 (m, 2 H), 1.80 (br s, 1 H), 2.18 (td, J = 7.0, 2.0 Hz, 2 H), 3.09–3.11 (m, 2 H), 4.67 (tt, J = 7.0, 2.0 Hz, 1 H), 7.11 (ddd, J = 7.5, 7.5, 1.5 Hz, 1 H), 7.25 (ddd, J = 7.5, 7.5, 1.0 Hz, 1 H), 7.34 (dd, J = 7.5, 1.5 Hz, 1 H), 7.54 (dd, J = 7.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 13.98 (q'), 18.70 (t'), 22.21 (t'), 28.24 (t'), 31.04 (t'), 44.60 (t'), 62.09 (d'), 80.31 (s'), 86.74 (s'), 124.99 (s'), 127.24 (d'), 128.47 (d'), 132.21 (d'), 132.82 (d'), 136.65 (s'); exact mass *m/z* calcd for $C_{15}H_{19}{}^{81}BrO$ 296.0599, found 296.0597. Anal. Calcd for $C_{15}H_{19}BrO$: C, 61.03; H, 6.49. Found: C, 60.90; H, 6.38.

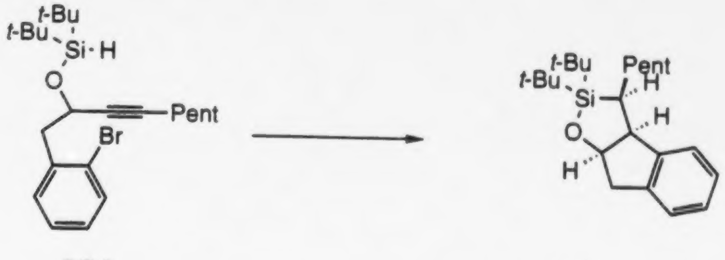
{2-[1-(2-Bromophenyl)3-nonynyl]oxy}di-*tert*-butylsilane (372).



373 **374**

The general procedure for silylation of alkynols was followed, using alcohol **373** (316.4 mg, 1.07 mmol), imidazole (146 mg, 2.14 mmol) in THF (9 mL), and *t*-Bu_2SiHCl (316.4 mg, 1.77 mmol) in THF (1 mL plus 1 mL as a rinse). The mixture was heated for 2 h. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 14 cm), using 1:99 Et_2O–hexane, gave silyl ether **374** (412.8 mg, 88%) as a pure [^1H NMR (400 MHz)], colorless oil: FTIR ($CHCl_3$ cast) 2960, 2931, 2857, 2098, 1471, 1069, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81–0.93 (m, 12 H), 1.02 (s, 9 H), 1.22–1.36 (m, 4 H), 1.38–1.49 (m, 2 H), 2.16 (td, J = 7.0, 2.0 Hz, 2 H), 3.05 (dd, J = 13.0, 7.0 Hz, 1 H), 3.21 (dd, J = 13.0, 7.0 Hz, 1 H), 4.08 (s, 1 H), 4.73 (tt, J = 7.0. 2.0 Hz, 1 H), 7.06 (td, J = 8.0, 1.5 Hz, 1 H), 7.20 (td, J = 7.5, 1.0 Hz, 1 H), 7.33 (dd, J = 7.5, 1.5 Hz, 1 H), 7.51 (dd, J = 8.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 14.02 (q'), 18.69 (t'), 19.71 (s'), 20.06 (s'), 22.26 (t'), 27.23 (q'), 27.38 (q'), 28.29 (t'), 31.05 (t'), 45.36 (t'), 65.60 (d'), 80.47 (s'), 86.33 (s'), 124.97 (s'), 126.93 (d'), 128.22 (d'), 132.53 (d'), 132.89 (d'), 137.09 (s'); exact mass *m/z* calcd for $C_{19}H_{28}OSi^{81}Br$ $(M - C_4H_9)^+$ 381.1072, found 381.1074. Anal. Calcd for $C_{23}H_{37}BrOSi$: C, 63.14; H, 8.52; Br, 18.26. Found: C, 63.10; H, 8.60; Br, 18.39.

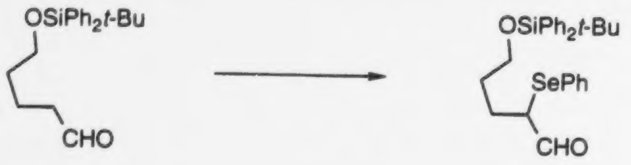
(±)-(3α,3aβ,8aβ)-2,2-Di-*tert*-butyl-4a,8a-dihydro-3-pentyl-4*H*-indeno[1,2,*d*][1,2]oxasilole (375).



374 **375**

The general procedure for radical cyclization was followed, using bromide **374** (131.1 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.15 mmol) in PhH (7.5 mL). Refluxing was continued for 30 min. after the stannane addition. After work up, flash chromatography of the residue over silica gel (1.8 × 17 cm), using increasing amounts of CH_2Cl_2 in hexane (from 10% to 20%), gave an oil that was purified by filtration through a pad of neutral alumina (0.5 × 2.5 cm), using hexane (*ca.* 10 mL), to give bicyclo **375** (97.7 mg, 91%) as a pure [^{1}H NMR (400 MHz)], colorless oil: FTIR ($CDCl_3$ cast) 2929, 2857, 1473, 1036, 914, 821, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.62 (s, 9 H), 0.92–0.99 (m, 3 H), 1.05 (s, 9 H), 1.33–1.61 (m, 5 H), 1.70–1.87 (m, 2 H), 1.92–2.00 (m, 1 H), 2.15–2.30 (m, 1 H), 3.01–3.16 (m, 2 H), 3.82 (dd, J = 8.5, 5.0 Hz, 1 H), 4.69 (t, J = 5.0 Hz, 1 H), 7.08–7.17 (m, 2 H), 7.23 (d, J = 7.5 Hz, 1 H), 7.33 (d, J = 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 14.24 (d'), 20.38 (s'), 21.78 (s'), 22.86 (t'), 27.17 (t'), 28.01 (q'), 28.28 (q'), 28.81 (d'), 31.70 (t'), 32.05 (t'), 41.54 (t'), 51.36 (d'), 82.33 (d'), 125.15 (d'), 126.03 (d'), 126.62 (d'), 126.68 (d'), 143.35(2 s'); exact mass m/z calcd for $C_{23}H_{38}OSi$ 358.2692, found 358.2678. Anal. Calcd for $C_{23}H_{28}OSi$: C, 77.03; H, 10.68. Found: C, 77.21; H, 10.92.

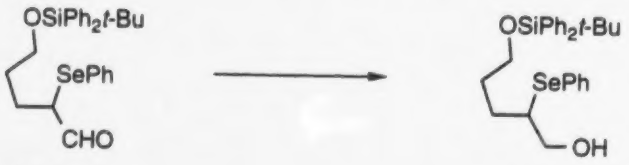
5-[(*tert*-Butyldiphenylsilyl)oxy]-2-(phenylseleno)-pentanal (387).



386 **387**

Dry Et_2NH (1.80 mL, 1.27 g, 1.7 mmol) was added to a stirred and cooled (0 °C) solution of PhSeCl (1.64 g, 8.56 mmol) in dry hexane (40 mL).[174] The red solution turned yellow and a precipitate was formed. Stirring was continued at 0 °C for 15 min, the cooling bath was removed, and the mixture was allowed to stand for 15 min. so that the precipitate settled. The supernatant layer was transferred by syringe to a stirred and cooled (-78 °C) solution of aldehyde **386** (2.62 g, 7.70 mmol) in dry CH_2Cl_2 (40 mL).[175] The residual salts were washed with dry hexane (20 mL), and the rinsings transferred, again by syringe, into the reaction mixture. Stirring was continued at -78 °C for 30 min, and saturated aqueous NaCl (100 mL) was added. The cooling bath was removed, and the mixture was allowed to reach room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using first 2:49 EtOAc–hexane, and then 1:9 EtOAc–hexane, gave an impure [^1H NMR (300 MHz)] oil, but was suitable for the next step.

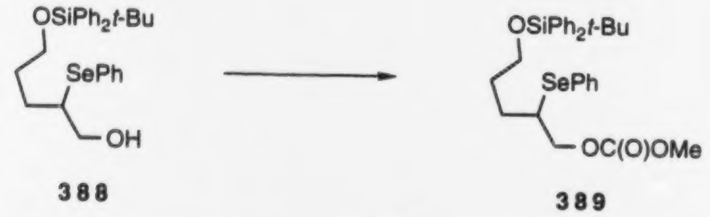
5-[(*tert*-Butyldiphenylsilyl)oxy]-2-(phenylseleno)-pentanol (387).



387 **388**

$NaBH_4$ (1.17 g, 3.1 mmol) was added in 10 portions (over *ca.* 10 min) to a stirred and cooled (0 °C) solution of aldehydes **386** and **387** in MeOH (75 mL). Stirring was continued at 0 °C for 1 h. Water (100 mL) was then added, the cooling bath was removed, and the mixture was acidified to *ca.* pH = 6, using AcOH (*ca.* 1 mL). The mixture was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 30 cm), using 1:9 EtOAc–hexane, gave alcohol **388** (1.8897 g, 49%) as a pure [^1H NMR (300 MHz)], slightly yellow oil: FTIR ($CDCl_3$ cast) 3432, 3070, 2931, 2857, 1111, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (s, 9 H), 1.58–1.94 (m, 4 H), 2.25 (br s, 1 H), 3.15–3.26 (m, 1 H), 3.50 (dd, J = 11.5, 6.5 Hz, 1 H), 3.60 (dd, J = 11.5, 5.0 Hz, 1 H), 3.64–3.72 (m, 2 H), 7.19–7.45 (m, 9 H), 7.49–7.56 (m, 2 H), 7.62–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.23 (s'), 26.91 (q'), 28.14 (t'), 30.71 (t'), 50.17 (d'), 63.43 (t'), 64.39 (t'), 127.28 (s'), 127.67 (s') (d'), 127.98 (d'), 129.11 (d'), 129.62 (d'), 133.89 (s'), 135.51 (d'), 135.59 (d'); exact mass *m/z* calcd for $C_{27}H_{34}O_2{}^{80}SeSi$ 498.1493, found 498.1493. Anal. Calcd for $C_{27}H_{34}O_2SeSi$: C, 65.17; H, 6.89. Found: C, 65.34; H, 6.96.

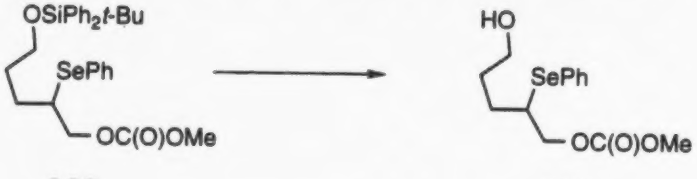
5-[(*tert*-Butyldiphenylsilyl)oxy]-2-(phenylseleno)-pentyl methyl carbonate (389).



CH_3OCOCl (0.55 mL, 7.1 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **388** (1 798.1 mg, 3.61 mmol) and dry pyridine (0.58 mL, 7.2 mmol) in dry CH_2Cl_2 (36 mL). Stirring was continued at 0 °C for 1 h, and the cooling the bath was then removed. CH_2Cl_2 (100 mL) was added and the mixture was washed with 10% aqueous $KHSO_4$ (50 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 25 cm), using 1:19 EtOAc–

hexane, gave methyl carbonate **389** (1 754.6 mg, 84%) as a pure [^{1}H NMR (400 MHz)], slightly yellow oil: FTIR ($CDCl_3$ cast) 2931, 1750, 1263, 1111, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.54–1.77 (m, 2 H), 1.85–1.98 (m, 2 H), 3.28–3.37 (m, 1 H), 3.64–3.70 (m, 2 H), 3.74 (s, 3 H), 4.19 (dd, *J* = 11.5, 8.5 Hz, 1 H), 4.33 (dd, *J* = 11.5, 5.5 Hz, 1 H), 7.23–7.32 (m, 3 H), 7.35–7.46 (m, 6 H), 7.53–7.58 (m, 2 H), 7.64–7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.25 (s'), 26.01 (q'), 28.13 (t'), 30.53 (t'), 42.97 (q'), 54.82 (d'), 63.37 (t'), 70.59 (t'), 127.69 (d'), 127.80 (s'), 127.98 (d'), 129.17 (d'), 129.63 (d'), 133.93 (s'), 135.22 (d'), 135.62 (d'), 155.60 (s'); exact mass *m/z* calcd for $C_{29}H_{36}O_4{}^{80}SeSi$ 556.1548, found 556.1553. Anal. Calcd for $C_{29}H_{36}O_4SeSi$: C, 62.69; H, 6.53. Found: C, 62.68; H, 6.50.

5-Hydroxy-2-(phenylseleno)pentyl methyl carbonate (390).

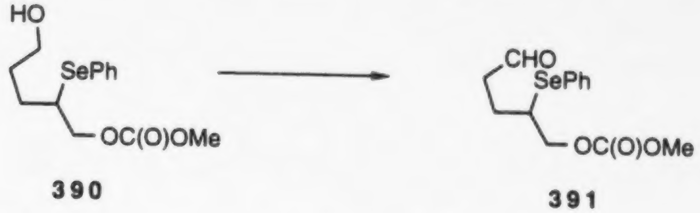


389 **390**

n-Bu_4NF[178] (3.88 mL, 1.0 M in THF, 3.88 mmol) was added to a stirred solution of silyl ether **389** (1 707.1 mg, 3.07 mmol) and glacial AcOH (0.22 mL, 3.84 mmol) in dry THF (28 mL). Stirring was continued for 22 h, and the mixture was then evaporated. Flash chromatography of the residue over silica gel (2.8 × 19 cm), using 2:3 EtOAc–hexane, gave alcohol **390** (928.8 mg, 95%) as a pure [^{1}H NMR (400 MHz)], slightly yellow oil: FTIR ($CHCl_3$ cast) 3382, 2953, 1748, 1439, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54–1.78 (m, 3 H), 1.83–1.97 (m, 2 H), 3.30–3.49 (m, 1 H), 3.66 (t, *J* = 6.0 Hz, 2 H), 3.75 (s, 3 H), 4.22 (dd, *J* = 11.0, 8.5 Hz, 1 H), 4.36 (dd, *J* = 11.0, 5.0 Hz, 1 H), 7.24–7.34 (m, 3 H), 7.56–7.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 28.06 (t'), 30.66 (t'), 42.94 (d'), 54.84 (q'), 62.38 (t'), 70.55 (t'), 127.74 (s'), 128.03 (d'), 128.10 (d'), 135.10 (d'), 155.52 (s'); exact mass *m/z* calcd for $C_{13}H_{18}O_4{}^{80}Se$

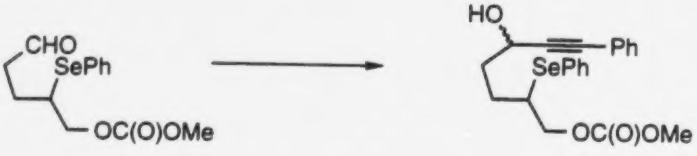
318.0370, found 318.0369. Anal. Calcd for $C_{13}H_{18}O_4Se$: C, 49.22; H, 5.72. Found: C, 49.10; H, 5.71.,

5-Oxo-2-(phenylseleno)pentyl methyl carbonate (391).



Dry DMSO (0.49 mL, 6.88 mmol) was added dropwise to a stirred and cooled (-63 °C) solution of $(COCl)_2$ (0.30 mL, 3.44 mmol) in dry CH_2Cl_2 (10 mL). Stirring was continued for 10 min, and a solution of alcohol **390** (876.7 mg, 2.76 mmol) in CH_2Cl_2 (2.5 mL plus 2.5 mL as a rinse) was added over 5 min. Stirring was continued for 15 min, and dry Et_3N (2.07 mL, 14.9 mmol) was added. Stirring was continued for 5 min, the cooling bath was removed, and the mixture was allowed to reach room temperature. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 18 cm), using 1:4 EtOAc–hexane, gave the aldehyde **391** (585.7 mg, 67%) as a pure [^1H NMR (400 MHz)], slightly yellow oil: FTIR ($CHCl_3$ cast) 1749, 1723, 1439, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.73–1.86 (m, 1 H), 2.13–2.25 (m, 1 H), 2.65–2.76 (m, 1 H), 2.77–2.87 (m, 1 H), 3.76 (s, 3 H), 4.09 (dd, J = 11.0, 8.5 Hz, 1 H), 4.40 (dd, J = 11.0, 5.0 Hz, 1 H), 7.25–7.36 (m, 3 H), 7.54–7.60 (m, 2 H), 9.79 (t, J = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 24.10 (t'), 41.99 (t'), 42.40 (d'), 54.92 (t'), 127.22 (s'), 128.30 (d'), 135.20 (d'), 155.46 (s'), 200.96 (d'); exact mass *m/z* calcd for $C_{13}H_{16}O_4{}^{80}Se$ 316.0214, found 316.0212. Anal. Calcd for $C_{13}H_{16}O_4Se$: C, 49.53; H, 5.12. Found: C, 49.74; H, 5.22.

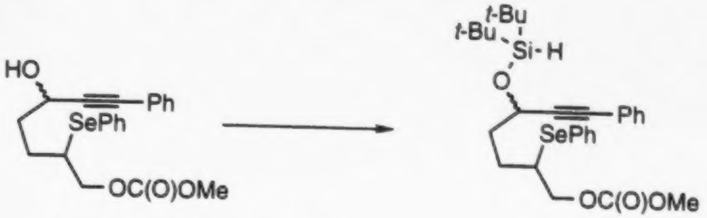
5-Hydroxy-7-phenyl-2-(phenylseleno)-6-heptynyl methyl carbonate (376).



391 **376**

The general procedure for addition of an acetylide to an aldehyde was followed, using phenylacetylene **268** (210 mg, 2.06 mmol) in THF (12 mL), *n*-BuLi (1.18 mL, 1.6 M in hexanes, 1.89 mmol), an initial reaction period of 15 minutes, and aldehyde **391** (540.9 mg, 1.72 mmol) in THF (2.5 mL plus 2.5 mL as a rinse). 10% Aqueous $KHSO_4$ (5 mL) was used to quench the reaction mixture. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 20 cm), using increasing amounts of EtOAc–hexane (from 15% to 25%), gave alcohols **376** (493.5 mg, 69%) as a inseparable [TLC, silica, EtOAc–hexane (1:9)], isomeric mixture [^{1}H NMR (400 MHz)]: FTIR ($CHCl_3$ cast) 3440, 3056, 1748, 1441, 1266, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68–1.85 (m, 1 H), 1.91–2.23 (m, 3 H), 2.30 (br s, 1 H), 3.32–3.43 (m, 1 H), 3.72 (two s, 3 H), 4.21 and 4.22 (two dd, *J* = 11.0, 6.5 Hz, 1 H), 4.36 and 4.37 (two dd, *J* = 11.0, 5.0 Hz, 1 H), 4.60–4.68 (m, 1 H), 7.19–7.35 (m, 6 H), 7.38–7.46 (m, 2 H), 7.57–7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 27.12 (t'), 27.33 (t'), 35.61 (t'), 35.68 (t'), 42.64 (d'), 42.69 (d'), 54.79 (q'), 62.34 (d'), 62.45 (d'), 70.46 (t'), 85.19 (s'), 85.27 (s'), 89.57, 89.64 (s'), 122.43 (s'), 127.40 (s'), 127.46 (s'), 128.03 (d'), 128.25 (d'), 128.43 (d'), 129.13 (d'), 131.96 (d'), 135.23 (d'), 135.26 (d'), 155.49 (s'); exact mass *m/z* calcd for $C_{21}H_{22}O_4{}^{80}Se$ 418.0683, found 418.0667. Anal. Calcd for $C_{21}H_{22}O_4Se$: C, 60.43; H, 5.31. Found: C, 60.29; H, 5.28

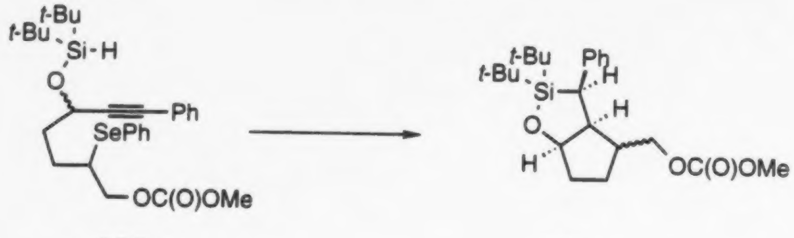
5-[(Di-*tert*-butylsilyl)oxy]-7-phenyl-2-(phenylseleno)-6-heptynyl methyl carbonate (377).



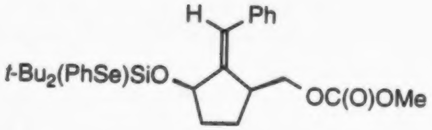
376 **377**

The general procedure for silylation of alkynols was followed, using alcohol **376** (443.5 mg, 1.06 mmol), imidazole (144.7 mg, 2.13 mmol) in THF (9 mL), and *t*-Bu_2SiHCl (228.0 mg, 1.28 mmol) in THF (1 mL plus 1 mL as a rinse). The mixture was heated for 1.75 h. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 × 15 cm), using 3:97 EtOAc–hexane, gave silyl ether **377** (522.3 mg, 88%) as a mixture of isomers [^1H NMR (400 MHz)]: FTIR ($CHCl_3$ cast) 2957, 2930, 2856, 2096, 1751, 1263, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 and 1.02 (two s, 9 H), 1.06 (two s, 9 H), 1.73–1.86 (m, 1 H), 1.90–2.00 (m, 1 H), 2.05–2.23 (m, 2 H), 3.34–3.43 (m, 1 H), 3.72 and 3.73 (two s, 3 H), 4.14 (two s, 1 H), 4.22 and 4.24 (2 dd, J = 11.0, 3.0 Hz, 1 H), 4.38 (dd, J = 11.0, 5.5 Hz, 1 H), 4.70–4.76 (m, 1 H), 7.20–7.33 (m, 6 H), 7.38–7.44 (m, 2 H), 7.57–7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.85 (s'), 20.19 (s'), 27.01 (t'), 27.19 (t'), 27.37 (q'), 27.40 (q'), 36.29 (t'), 36.41 (t'), 42.83 (d'), 42.91 (d'), 54.82 (q'), 66.25 (d'), 66.32 (d'), 70.32 (t'), 85.39 (s'), 89.85 (s'), 123.01 (s'), 127.62 (s'), 128.06 (d'), 128.26 (d'), 129.19 (d'), 131.65 (d'), 135.35 (d'), 135.38 (d'), 155.61 (s'); exact mass *m/z* calcd for $C_{29}H_{40}O_4{}^{80}SeSi$ 560.1861, found 560.1856. Anal. Calcd for $C_{29}H_{40}O_4SeSi$: C, 62.24; H, 7.20. Found: C, 62.27; H, 7.37.

Radical cyclization of methyl carbonate (377).



377 **378**



392

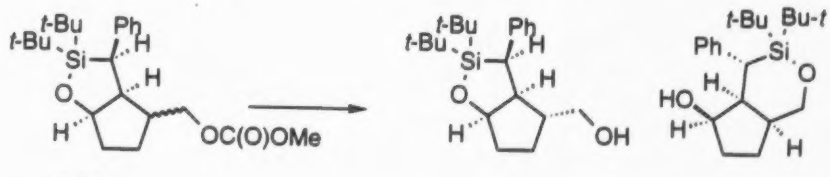
The general procedure for radical cyclization was followed, using selenide **377** (167.9 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5 mL), and AIBN (24.6 mg, 0.15 mmol) in PhH (7.5 mL). Refluxing was continued for 30 min. after the stannane addition. After workup, flash chromatography of the residue over silica gel (1.8 × 17 cm), using increasing amounts of CH_2Cl_2 in hexane (from 1% to 5%, 1% increment), gave **392** (50.4 mg, 30%) as a slightly impure [^{1}H NMR (400 MHz)], yellow oil, single isomer, and compounds **378** (82.1 mg, 67%) as a mixture of two isomers [^{1}H NMR (400 MHz)].

Selenide **392** has: FTIR ($CHCl_3$ cast) 2956, 2858, 1749, 1268 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 18 H), 1.78–2.01 (m, 4 H), 3.46–3.57 (m, 1 H), 3.76 (s, 3 H), 3.98 (dd, J = 10.5, 10.5 Hz, 1 H), 4.31 (dd, J = 10.5, 4.5 Hz, 1 H), 5.06–5.12 (m, 1 H), 6.72–6.75 (m, 1 H), 7.11–7.29 (m, 4 H), 7.30–7.44 (m, 4 H), 7.69–7.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 24.90 (q'), 25.04 (q'), 26.92 (t'), 28.52 (s'), 33.21 (t'), 38.98 (d'), 54.71 (d'), 69.57 (t'), 80.30 (q'), 124.84 (s'), 127.26 (d'), 127.31 (d'), 128.05 (d'), 128.40 (d'), 128.60 (d'), 128.63 (d'), 136.63 (s'), 137.77 (d'), 144.13 (s'), 155.75 (s'); exact mass m/z calcd for $C_{27}H_{36}O^{80}SeSi$ 484.1701, found 484.1699.

The mixture of isomers **378** has: FTIR ($CHCl_3$ cast) 2956, 2859, 1749, 1269 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 1.5 H), 1.07 (s, 6.5 H), 1.08 (s, 2.5 H), 1.13 (s, 6.5 H), 1.47–2.68 (m, 6 H), 3.16–3.33 (m, 1 H), 3.61–3.81 (m, 5 H), 4.52–4.58 (m, 0.72 H), 4.68 (m, 0.28 H), 7.12–7.20 (m, 1 H), 7.21–7.33 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 21.22 (s'), 21.58* (s'), 22.49* (s'), 22.67 (s'), 28.25* (q'), 28.30 (t'), 28.39 (q'), 28.68 (q'), 29.27* (q'), 33.43* (t'), 33.69 (t'), 34.30* (d'), 37.11 (d'), 39.23 (d'), 41.01* (t'), 48.62* (d'), 51.29 (d'), 54.50* (d'), 54.61 (d'), 68.93* (t'), 71.81 (t'), 83.56* (d'), 84.16 (d'), 125.38* (d'), 125.50 (d'), 128.28* (d'), 128.38 (d'), 129.86* (d'), 130.37 (d'), 140.38 (s'), 141.01* (s'), 155.54* (s'), 155.76 (s'); exact mass *m/z* calcd for $C_{23}H_{36}O_4Si$ 404.2383, found 404.2388. Anal. Calcd for $C_{23}H_{36}O_4Si$: C, 68.27; H, 8.97. Found: C, 68.18; H, 9.01.

* Signal associated with the minor isomer.

(±)-(3α,3aβ,4β,6β)-2,2-Di-*tert*-butyl-3,3a,4,5,6,6a-hexahydro-4-hydroxymethyl-3-phenyl-*2H*-cyclopent[*d*][1,2]oxasilole (393) and (±)-(4α,4aα,7β,7aα)-3,3-Di-*tert*-butyl-1,3,4,4a,5,6,7,7a-octahydro-5-hydroxy-4-phenyl-cyclopent[*d*][1,2]oxasilin (394).



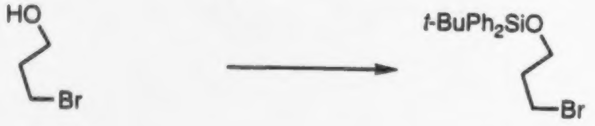
378 **393** **394**

Anhydrous K_2CO_3 (24.5 mg, 0.18 mmol) was added to a stirred solution of carbonates **378** (71.7 mg, 0.18 mmol) in MeOH (18 mL). Stirring was continued at room temperature for 3 days, and the mixture was evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using increasing amounts of EtOAc in hexane (from 5% to 20%), gave secondary alcohol **394** (16.7 mg, 27 %) and primary alcohol **393** (41.3 mg, 67%).

The secondary alcohol **394** has: mp 120–121.5 °C; FTIR (CHCl$_3$ cast) 3447, 2950, 2933, 2858, 1472, 1076, 1065, 821, 760, 701 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.04 (s, 1 H), 1.07 (s, 1 H), 1.24–1.55 (m, 3 H), 1.68–1.77 (m, 1 H), 1.77–1.86 (m, 1 H), 2.43–2.57 (m, 1 H), 2.65 (ddd, *J* = 13.0, 11.5, 4.0 Hz, 1 H), 3.19 (d, *J* = 13.0 Hz, 1 H), 3.63 (dd, *J* = 11.5, 11.5 Hz, 1 H), 4.87–4.95 (m, 2 H), 7.09–7.16 (m, 1 H), 7.22–7.30 (m, 2 H), 7.36–7.43 (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.468 MHz) δ 22.42 (s'), 23.09 (s'), 26.11 (t'), 26.67 (d'), 28.66 (q'), 28.80 (q'), 33.73 (t'), 40.44 (d'), 47.81 (d'), 67.52 (t'), 73.92 (d'), 125.09 (d'), 128.44 (d'), 129.21 (d'), 143.18 (s'); exact mass *m/z* calcd for $C_{21}H_{34}O_2Si$ 346.2328, found 346.2332.

The primary alcohol **393** has: FTIR (CHCl$_3$ cast) 3418, 2936, 2859, 1475, 1036, 990, 820, 701 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.08 (s, 9 H), 1.12 (s, 9 H), 1.21 (br s, 1 H), 1.47–1.57 (m, 1 H), 1.77–1.88 (m, 1 H), 1.88–1.97 (m, 1 H), 2.02–2.15 (m, 1 H), 2.21–2.32 (m, 1 H), 2.45–2.53 (m, 1 H), 3.09 (dd, *J* = 10.5, 8.0 Hz, 1 H), 3.26 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.29 (d, *J* = 8.0 Hz, 1 H), 4.54 (ddd, *J* = 5.0, 5.0, 2.5 Hz, 1 H), 7.13–7.18 (m, 1 H), 7.23–7.36 (m, 4 H); ^{13}C NMR (CDCl$_3$, 75.468 MHz) δ 21.25 (s'), 22.68 (s'), 27.92 (t'), 28.43 (q'), 28.69 (q'), 33.73 (t'), 37.34 (d'), 42.36 (d'), 67.12 (t'), 84.43 (d'), 125.43 (t'), 128.30 (t'), 130.48 (t'), 140.99 (s'); exact mass *m/z* calcd for $C_{21}H_{34}O_2Si$ 346.2328, found 346.2336.

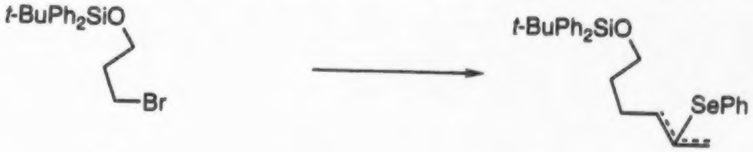
(3-Bromopropoxy)-*tert*-butyldiphenylsilane (396).



395 **396**

A solution of *t*-Bu$_2$SiHCl (2.88 mg, 10.5 mmol) in dry THF (2 mL plus 2 mL as a rinse) was added to a stirred solution of 3-bromo-propanol[109a] **395** (1.39 g, 10.0 mmol) and imidazole (0.75 g, 11.0 mmol) in dry THF (16 mL). The mixture was stirred at room temperature overnight. Water (50 mL) was added, and the mixture was extracted with ether (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 16), using 1:19 ether–hexanes, gave silyl ether **396** (3.21 g, 85%) as a colorless oil : FTIR ($CDCl_3$ cast) 3071, 2958, 2930, 2857, 1472, 1429, 1112, 701, 506 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 2.02–2.11 (m, 2 H), 3.68 (t, J = 6.5 Hz, 2 H), 3.78 (t, J = 5.5 Hz, 2 H), 7.34–7.46 (m, 6 H), 7.63–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 19.28 (s'), 26.88 (q'), 30.58 (t'), 35.54 (t'), 61.39 (t'), 127.74 (d'), 129.73 (d'), 133.63 (s'), 135.60 (d'). Anal. Calcd for $C_{19}H_{25}BrOSi$: C, 60.47; H, 6.68. Found: C, 60.68; H, 6.91.

Alkylation of (3-bromopropoxy)-*tert*-butyldiphenylsilane (396).

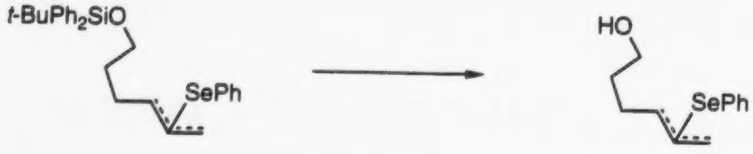


396

397

n-BuLi (0.78 mL, 1.6 M in hexanes, 1.25 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of dry *i*-Pr_2NH (132 mg, 1.3 mmol) in dry THF (10 mL). Stirring was continued for 15 min, and a solution of allyl phenylselenide[181] (127 mg, 1.20 mmol) in dry THF (1.5 mL plus 1.0 mL as a rinse) was added.[182] Stirring was continued at -78 °C for 15 min, and a solution of bromide **396** (377.4 mg, 1.00 mmol) in THF (1.5 mL plus 1.0 mL as a rinse) was added. Stirring was continued at -78 °C for 15 min. Saturated aqueous NH_4Cl (1 mL) was added, the cooling bath was removed, and the mixture was allowed to reach room temperature. Water (50 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 16 cm), using increasing amounts of EtOAc in hexanes (from 1% to 2%), gave of allylic selenides **397** (466.3 mg, 94%) as a mixture of isomers [^1H NMR (400 MHz)], suitable for the next step: FTIR ($CDCl_3$ cast) 2930, 2857, 1427, 1111, 736, 701, 690, 614, 505, 490 cm^{-1}; exact mass *m/z* calcd for $C_{28}H_{34}O^{80}SeSi$ 494.1544, found 494.1544. Anal. Calcd for $C_{28}H_{34}OSeSi$: C, 68.13; H, 6.94. Found: C, 68.12; H, 6.79.

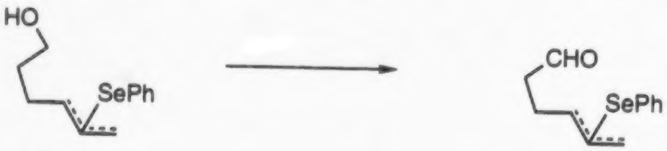
Cleavage of the silicon group from silyl ether (397).



397 **398**

n-Bu_4NF[178] (0.77 mL, 1.0 M in THF, 0.77 mmol) was added to a stirred solution of silyl ether **397** (345.1 mg, 0.70 mmol) in dry THF (14 mL). Stirring was continued at room temperature for 1.5 h, water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (1 × 80 mL, 2 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 15 cm), using 1:4 EtOAc–hexane, gave alcohol **398** (167.6 mg, 94%) as a mixture of isomers [^{1}H NMR (400 MHz)], but suitable for the next step: FTIR ($CDCl_3$ cast) 3346, 2935, 1476, 1437, 1058, 1022, 738, 691 cm^{-1}; exact mass *m/z* calcd for $C_{12}H_{16}O^{80}Se$ 256.0366, found 256.0362. Anal. Calcd for $C_{12}H_{16}OSe$: C, 56.47; H, 6.32. Found: C, 56.70; H, 6.39.

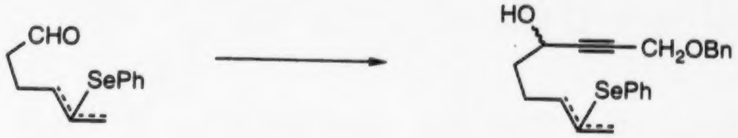
Oxidation of alcohol (398).



398 **399**

Ph_3BiCO_3[187] (0.79 g, 1.58 mmol) was tipped into a solution of alcohol **398** (127.6 mg, 0.50 mmol) in dry $PhCH_3$ (13 mL). Pyridine (0.85 mL, 10 mmol) was added, and the suspension was heated at 80 °C for 24 h. The mixture was cooled to room temperature, and anhydrous Et_2O (20 mL) was added. The mixture was filtered through a pad of Celite (10 × 2.5 cm), the pad was washed with Et_2O (2 × 10 mL), and the combined filtrates were evaporated, first under water-pump vacuum, and then under oil-pump vacuum (to remove most of the pyridine). Flash chromatography of the residue over silica gel (1.8 × 8), using 1:19 EtOAc–hexane, gave aldehydes **399** (44.6 mg, 35%) as a deep yellow oil: FTIR ($CDCl_3$ cast) 3056, 2929, 2823, 2721, 1723, 1477, 1437, 738, 692 cm^{-1}; exact mass *m/z* calcd for $C_{12}H_{14}O^{80}Se$ 254.0210, found 254.0208.

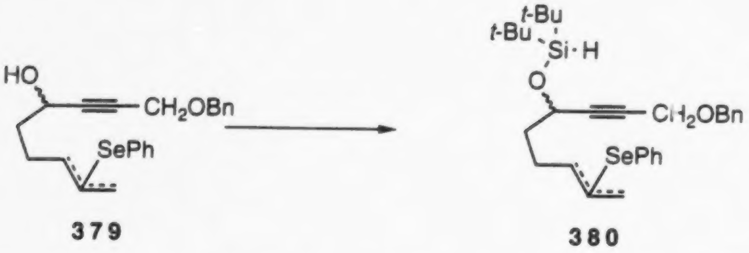
Coupling of aldehyde 399 with acetylene 318 (R' = CH_2OBn).



399 **379**

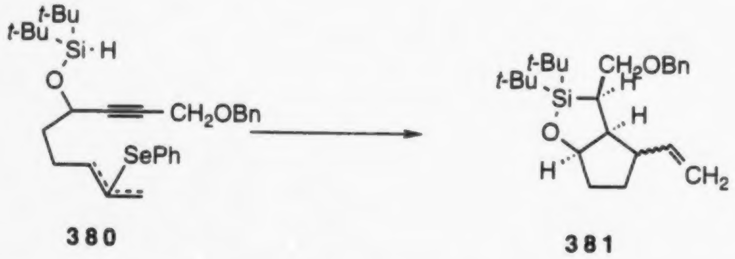
The general procedure for addition of an acetylide to an aldehyde was followed, using 3-benzyloxypropyne **318** (R' = CH_2OBn) (188 mg, 1.29 mmol) in THF (12 mL), *n*-BuLi (0.75 mL, 1.6 M in hexanes, 1.2 mmol), an initial reaction period of 10 min aldehyde **399** (217.4 mg, 0.86 mmol) in THF (2.5 mL plus 2.5 mL as a rinse). Stirring was continued for 15 min. Water (40 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.8 × 18 cm), using increasing amounts of EtOAc in hexane (from 10% to 20%), gave alcohol **379** (226.4 mg, 66%) as a yellow oil. The mixture of isomers has FTIR ($CDCl_3$ cast) 3410, 2927, 2855, 1477, 1437, 1072, 1022, 737, 692 cm^{-1}; exact mass *m/z* calcd for $C_{22}H_{24}O_2{}^{80}Se$ 400.0942, found 400.0940. Anal. Calcd for $C_{22}H_{24}O_2Se$: C, 66.16; H, 6.06. Found: C, 66.18; H, 6.06.

Silylation of alcohol (379).



The general procedure for silylation of alkynols was followed, using alcohol **379** (565.9 mg, 1.42 mmol), imidazole (193 mg, 2.83 mmol) in THF (10 mL), and t-Bu_2SiHCl (304 mg, 1.70 mmol) in THF (2 mL plus 2 mL). The mixture was heated for 2.25 h. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 × 15 cm), using increasing amounts of Et_2O in hexane (from 2% to 4 %), gave silyl ether **380** (594.7 mg, 77%) as a yellowish oil. The mixture of isomers has: FTIR ($CDCl_3$ cast) 2930, 2856, 2094, 1470, 1089, 825, 736 cm^{-1}; exact mass *m/z* calcd for $C_{30}H_{42}O_2{}^{80}SeSi$ 542.2119, found 542.2123. Anal. Calcd for $C_{30}H_{42}O_2SeSi$: C, 66.52; H, 7.81. Found: C, 66.46; H, 7.93.

(±)-(3α,3aβ,4α,6β)-Hexahydro-2,2-di(1,1-dimethylethyl)-3-phenyl-4-vinyl-2*H*-cyclopent[*d*][1,2]oxasilole and (±)-(3α,3aβ,4β,6β)-hexahydro-2,2-di(1,1-dimethylethyl)-3-phenyl-4-vinyl-2*H*-cyclopent[*d*][1,2]oxasilole (381).



The general procedure for radical cyclization was followed, using selenide **380** (162.5 mg, 0.30 mmol) in PhH (45 mL), Ph_3SnH (210.6 mg, 0.60 mmol) in PhH (7.5

mL), and AIBN (24.6 mg, 0.15 mmol) in PhH (7.5 mL). Refluxing was continued for 2 h after the stannane addition. After workup, flash chromatography of the residue over silica gel (1.8 × 15 cm), using increasing amounts of CH_2Cl_2 in hexane (from 20% to 40%), gave bicyclo **381** (34.6 mg, 30%) as a [^{1}H NMR (400 MHz)], colorless oil, contaminated (ca. 10%) by a unidentified compound. The mixture (3:1) of isomers **381** had: FTIR ($CDCl_3$ cast) 2933, 2857, 1474, 1093, 1071, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (s, 9 H), 1.06 (s, 9 H), 1.32–2.90 (series of m, 7 H), 3.69–4.60 (series of m, 5 H), 4.86-4.94 (2 m, 1 H), 4.96–5.04 (2 m, 1 H), 5.81 (ddd, *J* = 18.0, 10.0, 8.5 Hz, 0.75 H), 6.24 (ddd, *J* = 18.0, 10.0, 10.0 Hz, 0.25 H), 7.25–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.468 MHz) δ 20.07 (s'), 21.61* (s'), 22.03 (s'), 22.37* (s'), 27.53* (q'), 2794 (q'), 28.22†,28.73 (q'), 29.15†, 29.30†, 44.98 (d'), 47.15* (d'), 48.44* (d'), 51.68 (d'), 68.78* (t'), 69.16 (t'), 72.44 (t'), 72.63* (t'), 83.29* (d'), 84.46 (d'), 112.27 (t'), 113.74* (t'), 127.44–128.36 (series of d'), 138.64 (s'), 138.79* (s'), 142.70* (d'), 143.86 (d'); exact mass *m/z* calcd for $C_{20}H_{29}O_2Si$ (M - C_4H_9)$^+$ 329.1937, found 329.1939. mass (CI) *m/z* calcd for $C_{24}H_{42}O_2NSi$ (M + 18)$^+$ 404, found 404.2.

* Belongs to the minor isomer.

† Could be either d' of major isomer or q' of minor isomer.

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(6) For detailed mechanisms of the reactions in this section, see the corresponding reviews.

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